NIHR | National Institute for Health and Care Research

Journals Library

Check for updates

Health Technology Assessment

Volume 29 • Issue 16 • May 2025

ISSN 2046-4924

Effectiveness of biomarker-guided duration of antibiotic treatment in children hospitalised with confirmed or suspected bacterial infection: the BATCH RCT

Cherry-Ann Waldron, Philip Pallmann, Simon Schoenbuchner, Debbie Harris, Lucy Brookes-Howell, Céu Mateus, Jolanta Bernatoniene, Katrina Cathie, Saul N Faust, Josie Henley, Lucy Hinds, Kerry Hood, Chao Huang, Sarah Jones, Sarah Kotecha, Sarah Milosevic, Helen Nabwera, Sanjay Patel, Stéphane Paulus, Colin VE Powell, Jenny Preston, Huasheng Xiang, Emma Thomas-Jones and Enitan D Carrol, on behalf of the BATCH trial team

DOI 10.3310/MBVA3675

NIHR | National Institute for Health and Care Research

Health Technology Assessment

Check for updates

Extended Research Article

Effectiveness of biomarker-guided duration of antibiotic treatment in children hospitalised with confirmed or suspected bacterial infection: the BATCH RCT

Cherry-Ann Waldron,[1*] Philip Pallmann,[1] Simon Schoenbuchner,[2] Debbie Harris,[1] Lucy Brookes-Howell,[1] Céu Mateus,[3] Jolanta Bernatoniene,[4] Katrina Cathie,[5,6,7] Saul N Faust,[5,6,7] Josie Henley,[8] Lucy Hinds,[9] Kerry Hood,[10] Chao Huang,[11] Sarah Jones,[12] Sarah Kotecha,[1] Sarah Milosevic,[1] Helen Nabwera,[13,14,15] Sanjay Patel,[5,7] Stéphane Paulus,[16,17] Colin VE Powell,[2] Jenny Preston,[18] Huasheng Xiang,[19,20] Emma Thomas-Jones[1†] and Enitan D Carrol[15,21†] on behalf of the BATCH trial team

[1]Centre for Trials Research, Cardiff University, Neuadd Meirionnydd, Heath Park, Cardiff, UK
[2]Division of Population Medicine, School of Medicine, Cardiff University, Heath Park, Cardiff, UK
[3]Division of Health Research, Lancaster University, Lancaster, UK
[4]University Hospitals Bristol and Weston NHS Foundation Trust, Bristol Royal Hospital for Children, Bristol, UK
[5]NIHR Southampton Clinical Research Facility and Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[6]Faculty of Medicine and Institute for Life Sciences, University of Southampton, Southampton, UK
[7]Department of Paediatric Infectious Diseases, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[8]School of Social Sciences, Cardiff University, Cardiff, UK
[9]Sheffield Children's NHS Foundation Trust, Sheffield, UK
[10]College of Biomedical Life Sciences, Cardiff University, Cardiff, UK
[11]Hull York Medical School, University of Hull, Hull, UK
[12]Involve Network, Health and Care Research Wales, Cardiff, UK
[13]Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, UK
[14]Centre of Excellence in Women and Child Health, Aga Khan University, Nairobi, Kenya
[15]Department of Infectious Diseases, Alder Hey Children's NHS Foundation Trust, Liverpool, UK
[16]Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[17]Department of Paediatrics, University of Oxford Oxford, UK
[18]NIHR Alder Hey Clinical Research Facility, Alder Hey Children's NHS Foundation Trust, Liverpool, UK
[19]Management School, Lancaster University, Lancaster, UK
[20]Lancaster University College at Beijing Jiaotong University, Shandong, China
[21]Department of Clinical Infection, Microbiology and Immunology, Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, Liverpool, UK

[†]Joint last authors

[*]**Corresponding author** waldronc@cardiff.ac.uk

Published May 2025
DOI: 10.3310/MBVA3675

This report should be referenced as follows:

Waldron C-A, Pallmann P, Schoenbuchner S, Harris D, Brookes-Howell L, Mateus C, *et al.* Effectiveness of biomarker-guided duration of antibiotic treatment in children hospitalised with confirmed or suspected bacterial infection: the BATCH RCT. *Health Technol Assess* 2025;29(16). https://doi.org/10.3310/MBVA3675

Health Technology Assessment

ISSN 2046-4924 (Online)

Impact factor: 3.5

A list of Journals Library editors can be found on the NIHR Journals Library website

Launched in 1997, *Health Technology Assessment* (HTA) has an impact factor of 3.5 and is ranked 30th (out of 174 titles) in the 'Health Care Sciences & Services' category of the Clarivate 2022 Journal Citation Reports (Science Edition). It is also indexed by MEDLINE, CINAHL (EBSCO Information Services, Ipswich, MA, USA), EMBASE (Elsevier, Amsterdam, the Netherlands), NCBI Bookshelf, DOAJ, Europe PMC, the Cochrane Library (John Wiley & Sons, Inc., Hoboken, NJ, USA), INAHTA, the British Nursing Index (ProQuest LLC, Ann Arbor, MI, USA), Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and the Science Citation Index Expanded™ (Clarivate™, Philadelphia, PA, USA).

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta.

Criteria for inclusion in the *Health Technology Assessment* journal

Manuscripts are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This article

The research reported in this issue of the journal was funded by the HTA programme as award number 15/188/42. The contractual start date was in September 2017. The draft manuscript began editorial review in February 2024 and was accepted for publication in October 2024. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' manuscript and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

This article presents independent research funded by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care.

This article was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Newgen Digitalworks Pvt Ltd, Chennai, India (www.newgen.co).

Abstract

Background: Procalcitonin is a biomarker specific for bacterial infection, with a more rapid response than other commonly used biomarkers, such as C-reactive protein, but it is not routinely used in the National Health Service.

Objective: To determine if using a procalcitonin-guided algorithm may safely reduce duration of antibiotic therapy compared to standard of care in hospitalised children with suspected or confirmed infection.

Design: A pragmatic, multicentre, open-label, parallel two-arm, individually randomised controlled trial with internal pilot phase, qualitative study and health economic evaluations.

Setting: Paediatric wards or paediatric intensive care units within children's hospitals (*n* = 6) and district general hospitals (*n* = 9) in the United Kingdom.

Participants: Children aged between 72 hours and 18 years admitted to hospital and being treated with intravenous antibiotics for suspected or confirmed bacterial infection.

Interventions: Procalcitonin-guided algorithm versus usual standard care alone.

Main outcome measures: Coprimary outcomes were duration of intravenous antibiotic use and a composite safety measure.

Results: Between 11 June 2018 and 12 October 2022, 1949 children were recruited: 977 to the procalcitonin group [427 female (43.7%), 550 male (56.3%)], and 972 to the usual care group [478 female (49.2%), 494 male (50.8%)]. Duration of intravenous antibiotics was not significantly different between the procalcitonin group (median 96.0 hours) and the usual care group (median 99.7 hours) [hazard ratio = 0.96 (0.87, 1.05)], and the procalcitonin-guided algorithm was non-inferior to usual care [risk difference = −0.81% (95% confidence interval upper bound 1.11%)]. At clinical review, a procalcitonin result was available for 81.8% of the time, which was considered as part of clinical decision-making 66.6% of the time, and the algorithm was adhered to 57.2% of the time. Incremental cost-effectiveness ratio per duration of intravenous antibiotics hour avoided from bootstrapped samples was £467.62 per intravenous antibiotic hour avoided. Cost analysis of complete cases was also higher in the procalcitonin arm for all age groups, and for children aged 5 years and over. The intervention is not cost-effective as it is more expensive with no significant improvement in intravenous antibiotic duration.

Limitations: Robust antimicrobial stewardship programmes were already implemented in the lead recruiting sites, and adherence to the algorithm was poor. Clinicians may be reluctant to adhere to biomarker-guided algorithms, due to unfamiliarity with interpreting the test result.

Conclusions: In children hospitalised with confirmed or suspected bacterial infection, the addition of a procalcitonin-guided algorithm to usual care is non-inferior in terms of safety, but does not reduce duration of intravenous antibiotics, and is not cost-effective. In the presence of robust antimicrobial stewardship programmes to reduce antibiotic use, a procalcitonin-guided algorithm may offer little added value.

Future work: Future trials must include an implementation framework to improve trial intervention fidelity, and repeated cycles of education and training to facilitate implementation of biomarker-guided algorithms into routine clinical care.

Trial registration: This trial is registered as ISRCTN11369832.

Funding: This award was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR award ref: 15/188/42) and is published in full in *Health Technology Assessment*; Vol. 29, No. 16. See the NIHR Funding and Awards website for further award information.

Contents

List of tables

List of figures

List of abbreviations

AAU	Acute Assessment Unit
A&E	accident and emergency
ADAPT-Sepsis	BiomArker-guided Duration of Antibiotic treatment in hospitalised PaTients with suspected Sepsis
ADR	adverse drug reaction
AE	adverse event
AMR	antimicrobial resistance
AMS	antimicrobial stewardship
APPG	All-Party Parliamentary Group
BNF	British National Formulary
CACE	complier-average causal effect
CFIR	Consolidated Framework for Implementation Research
CHU9D	Child Health Utility 9D questionnaire
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRN	Clinical Research Network
CRP	C-reactive protein
CSF	cerebrospinal fluid
CT	computed tomography
CTR	Centre for Trials Research
ED	emergency department
ENT	ear, nose and throat
GBP	Great British pounds
GCP	good clinical practice
GDPR	General Data Protection Regulation
GP	general practitioner
HAI	hospital-acquired infection
HCP	healthcare professional
HR	hazard ratio
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
ID	infectious disease
IDMC	Independent Data Monitoring Committee
ISRCTN	International Standard Randomised Controlled Trial Number
IV	intravenous
LRT	likelihood-ratio test
LRTI	lower respiratory tract infection
MICE	multiple imputation with chained equations
MRI	magnetic resonance imaging
NeoPINS	Neonatal PCT Intervention Study
NICE	National Institute for Health and Care Excellence
NICU	neonatal intensive care units
NHDU	neonatal high dependency units
NIHR	National Institute for Health and Care Research
OPAT	outpatient parenteral antibiotic therapy
OR	odds ratio
PCT	procalcitonin
PH	proportional hazards
PHDU	paediatric high dependency unit
PI	principal investigator
PICU	paediatric intensive care unit
PID	participant identification
PIMS-TS	paediatric multisystem inflammatory syndrome temporally associated with COVID-19
PIS	participant information sheet
PPI	patient and public involvement
PPIE	patient and public involvement and engagement
PRONTO	PROcalcitonin and NEWS2 evaluation for Timely identification of sepsis and Optimal use of antibiotics in the emergency department

PRORATA	PROcalcitonin to Reduce Antibiotic Treatments in Acutely ill patients
PROSACAB	PROcalcitonin to Stop Antibiotics after CArdiovascular surgery in a pediatric intensive care unit
QALYs	quality-adjusted life-years
R&D	Research and Development
RCT	randomised controlled trial
RD	risk difference
REC	Research Ethics Committee
SACE	survivor average causal effects
SAE	serious adverse event
SBI	serious bacterial infection
SCBU	special care baby units
SWAP	study within a project
TSC	Trial Steering Committee
UC	usual care
UKECA	United Kingdom Ethics Committee Authority
YPAG	Young People's Advisory Group

Plain language summary

A daily task in hospitals is to assess whether sick children have an infection or not, and doctors need to decide whether to start, stop or change antibiotics. On one hand, giving antibiotics promptly saves lives, but on the other, giving antibiotics to people who do not need them leads to overuse of antibiotics resulting in antibiotics no longer working for infections, so-called antibiotic resistance. If we can reduce antibiotic use in hospitals, this would be an important step in combating the spread of hospital superbugs.

Blood tests can be used to measure the body's response to infection. Most hospitals in the National Health Service use blood tests to monitor whether a person is responding to antibiotics. One example is C-reactive protein, but this test does not always tell you whether there is an infection there and if it is getting better, or whether the person is just unwell from another reason. A blood test measuring procalcitonin is better for diagnosing bacterial infections, and procalcitonin levels are quicker to decrease when a patient starts to improve and antibiotics start working, compared to C-reactive protein levels. However, procalcitonin tests are not routinely used for children in the National Health Service.

The BATCH trial looked at whether the use of a procalcitonin test is safe and could help doctors decide whether to stop or change antibiotics (from intravenous to oral), both of which safely reduce antibiotic use (and help limit antibiotic resistance), compared to not using the test.

The trial found that in children admitted to hospital with a bacterial infection, the addition of the procalcitonin test is safe to use but does not reduce how long intravenous antibiotics were given for.

Doctors did not always use the procalcitonin result when making antibiotic decisions, and although parents were largely positive about participation in the trial, some had concerns about extra blood tests and clinicians stopping antibiotics too early. Future research should include education and training for doctors to ensure that the procalcitonin test forms part of routine care.

Scientific summary

Background

The BATCH trial aimed to improve antimicrobial stewardship (AMS) in hospitalised children with suspected or confirmed bacterial infection, by reducing antibiotic duration with guidance from an additional procalcitonin (PCT) biomarker laboratory test. This trial aligns with the current Department of Health Five Year Strategy and is a response to research recommendations from two published National Institute for Health and Care Excellence (NICE) guidance documents (DG18 and NG15).

The trial was a pragmatic, multicentre, open-label, parallel two-arm, individually randomised controlled trial (RCT) with internal pilot phase, qualitative study and health economic evaluations. The trial assessed the use of an additional PCT test in children (aged 72 hours up to 18 years) hospitalised with suspected or confirmed infection to guide antimicrobial-prescribing decisions. In children randomised to the intervention arm, a PCT test was performed in the hospital laboratory at baseline/randomisation and every 1–3 days while on intravenous (IV) antibiotics. Children in the control arm did not have the PCT test performed.

Outcomes

The trial used a coprimary outcome of antibiotic use and safety.

- Duration of IV antibiotic use was measured in hours.
- Safety was defined as the absence of all of the following:
  - unscheduled admissions/re-admissions [to include re-admission within 7 days of discharge with infective diagnosis, unscheduled re-admission to paediatric intensive care unit (PICU) with infective diagnosis or admission to PICU with infective diagnosis].
  - retreatment for same condition within 7 days of stopping IV antibiotics (restarting IV antibiotics which have been stopped)
  - death for any reason in the 28 days following randomisation.

Secondary outcome measures

- Total duration of antibiotic use (IV and oral).
- Duration of broad-spectrum antibiotic use.
- Time to discharge from hospital.
- Suspected adverse drug reactions (ADRs) (yes or no).
- Cost of hospital episode.
- Hospital-acquired infections (HAIs) as defined by the clinical team up to day 28.
- Health utility as measured by the Child Health Utility questionnaire (CHU9D) up to day 28.
- To provide detailed understanding of parent and health professionals' attitudes to, and experiences of, participating in the BATCH RCT.

Methods

A pragmatic, multicentre, open-label, parallel two-arm, individually RCT conducted in 15 hospitals in the UK. Children aged between 72 hours and 18 years admitted to hospital and being treated with IV antibiotics for suspected or confirmed bacterial infection were randomised (1 : 1 ratio of allocation) using minimisation for age and centre and using a secure 24-hour web-based randomisation programme to a PCT-guided algorithm versus usual standard care alone.

The sample size of 1942 was determined, based on detecting a 1-day reduction in IV antibiotic use (90% power, two-sided) and on a non-inferiority margin of 5% absolute risk difference (RD) in the composite safety outcome (90% power, one-sided), while allowing for up to 10% loss to follow-up. Semistructured qualitative interviews were also carried out with parents and healthcare professionals (HCPs).

Health economics

Health economic analysis included direct and indirect costs associated with unscheduled admissions (to ward or PICU), re-admissions, restarting IV antibiotics and HAIs. Descriptive and regression analysis was used to identify key elements of service use and cost and explored the potential impact of baseline participant characteristics on the costs and outcomes measures. Average cost per participant was estimated at the end of the treatment and the follow-up periods, respectively, and average cost per subgroup of patients was explored for the same time points. Bootstrapping and missing data imputation were performed if justified. Differences in each arm were assessed and used for the computation of an incremental cost-effectiveness ratio (ICER). A cost-effectiveness analysis assessed possible efficiency gains. An NHS perspective was used, and relevant direct medical costs were collected. Time horizon was 28 days; therefore, there was no need to consider a discount rate. Patients' health utility was measured using CHU9D up to day 28. Descriptive and regression analysis was used to identify key elements of service use and cost and to explore the potential impact of baseline participant characteristics on the costs and outcomes measures. Differences in each arm were assessed and used for the computation of an ICER. Bootstrap sampling and a complete-case analysis were conducted to access the sensitivity of our main results. A cost-effectiveness plane was constructed. Information on direct non-medical costs, such as travelling to and from the hospitals, and indirect costs, such as parents' productivity losses, was also collected.

Results

There was no evidence of a treatment effect on any primary or secondary outcome, either overall or in any subgroup. The estimated treatment effect for the composite safety outcome was consistent with non-inferiority. We therefore conclude that making the results of the PCT-guided algorithm available to clinicians was non-inferior with respect to safety and ineffective with respect to antibiotic use.

The PCT test in itself is not very expensive (£14); nevertheless, it does not contribute to a reduction in the number of hours of IV antibiotic administration. The intervention is not cost-effective as it is more expensive with no significant improvement in IV antibiotic duration, even though it resulted in a non-significant improvement in health-related quality of life (HRQoL). Productivity losses are similar in both arms. It should be noted that income losses of around £200 during a child hospital stay are significant for families.

The qualitative evaluation showed that parent perceptions on acceptability and implementation of the intervention and trial processes were largely positive, although most parents were concerned about their child having to have extra blood tests if they were in the intervention arm. HCPs took a while to become familiar with the intervention algorithm, and as the intervention test did not align with the clinical pathway, often there were delays in getting the PCT results, which meant that adherence to the algorithm was low.

In children with comorbidities, HCPs were significantly more likely to take the PCT test into consideration, with increasing number of comorbidities, although for certain comorbidities HCPs were less likely to adhere to the algorithm. On interview, HCPs stated that antibiotic duration would likely be longer in children with comorbidities, but on quantitative analysis, there was no significant difference in antibiotic duration across comorbidity subgroups.

Conclusions

We demonstrated that there was no evidence of a treatment effect on any primary or secondary outcome, either overall or in any subgroup. The estimated treatment effect for the composite safety outcome was consistent with non-inferiority. We therefore conclude that making the results of the PCT-guided algorithm available to clinicians was non-inferior with

respect to safety and did not result in reduced antibiotic duration in hospitalised children with suspected or confirmed bacterial infection. Parental and HCP acceptability of the intervention was generally positive, although adherence was low, due to the intervention not being integrated into the routine care pathway.

Clinicians may be reluctant to adhere to biomarker-guided algorithms, due to unfamiliarity with interpreting the test result. In the presence of robust AMS programmes to reduce antibiotic use, a PCT-guided algorithm may offer little added value. Future trials must include an implementation framework to improve trial intervention fidelity, and repeated cycles of education and training to facilitate implementation of biomarker-guided algorithms into routine clinical care.

Trial registration

This trial is registered as ISRCTN11369832.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR award ref: 15/188/42) and is published in full in *Health Technology Assessment*; Vol. 29, No. 16. See the NIHR Funding and Awards website for further award information.

Chapter 1 Introduction

Importance of the problem

Sepsis

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection.[2] Sepsis causes many non-specific signs and symptoms that can also be caused by a large number of conditions that may or may not be due to infection, and that may or may not require immediate or urgent treatment. Sepsis is usually caused by bacteria, although viral and fungal causes do occur. The problem for clinicians is the difficulty in distinguishing bacterial sepsis from other conditions presenting with non-specific signs and symptoms. Prompt administration of antibiotics reduces mortality by half,[3] but indiscriminate antibiotic use increases antimicrobial resistance (AMR), resulting in increased costs for hospitalised patients.[4,5] Severe sepsis accounts for approximately 45% of intensive care unit (ICU) bed-days and 33% of hospital bed-days, representing a significant resource burden in the NHS. Not all children admitted with bacterial infection will meet the criteria for sepsis, but they could still have serious infection, requiring IV antibiotics for several days. In this study, we focused on children presenting with suspected or confirmed bacterial infections, including serious bacterial infections (SBIs) and sepsis.[1]

C-reactive protein and procalcitonin

Biomarker blood tests currently used in the NHS, such as C-reactive protein (CRP), do not reliably differentiate between SBIs and inflammation and show a delayed response (12–24 hours) to bacterial infection. Procalcitonin (PCT) is a biomarker released in response to inflammatory stimuli including bacterial infections, with very high levels produced in SBIs.[6] In contrast to CRP, PCT blood concentrations rise early (within 6–12 hours) and peak early, falling rapidly in response to effective antimicrobial therapy. This makes blood PCT potentially a better biomarker for monitoring progression of SBIs and response to antimicrobial therapy, and for informing initiation, change or discontinuation of antimicrobial therapy. A guideline from the NICE recommended further research on PCT testing to guide antibiotic use in children.[7] There are no evidence-based biomarker-guided algorithms to support AMS in adults or children, and a randomised controlled trial (RCT) was needed to determine if PCT can help deliver the shortest, safe duration of antibiotics to treat bacterial infections in children.

Antimicrobial resistance

Antimicrobial resistance is an increasing threat to the NHS quality and safety agenda. The lack of significant new antimicrobials in the development pipeline has led to increased pressure on existing antibiotics and greater challenges in treating patients with infections. Inappropriate use of antimicrobials increases the risk to patients of acquiring resistant organisms and subsequent transmission to other patients. The term 'antimicrobial stewardship' (AMS) is defined as 'an organisational or healthcare-system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness'. AMS is a fundamental component of the UK Department of Health Five Year Antimicrobial Resistance Strategy 2019–24[8] and the 20-year Vision.[9] A 'Start Smart – then Focus' approach is recommended for antibiotic prescribing in order to reduce AMR and improve patient safety (*Figure 1*).[10] National Institute for Health and Care Excellence (NICE) guidance on AMS recommends reviewing IV antimicrobial prescriptions at 48–72 hours including response to treatment and microbiological results, in order to determine if the antimicrobial needs to be continued and, if so, whether it can be switched to an oral antimicrobial.[11] The Five Year Antimicrobial Resistance Strategy aims to conserve and steward the effectiveness of existing antimicrobials by ensuring that antibiotics are used responsibly and less often.[8]

There is strong evidence for introducing paediatric AMS programmes in hospital settings in terms of reduced antibiotic use, improved quality of prescribing and costsavings. Long-term and sustainable reductions in antimicrobial prescribing

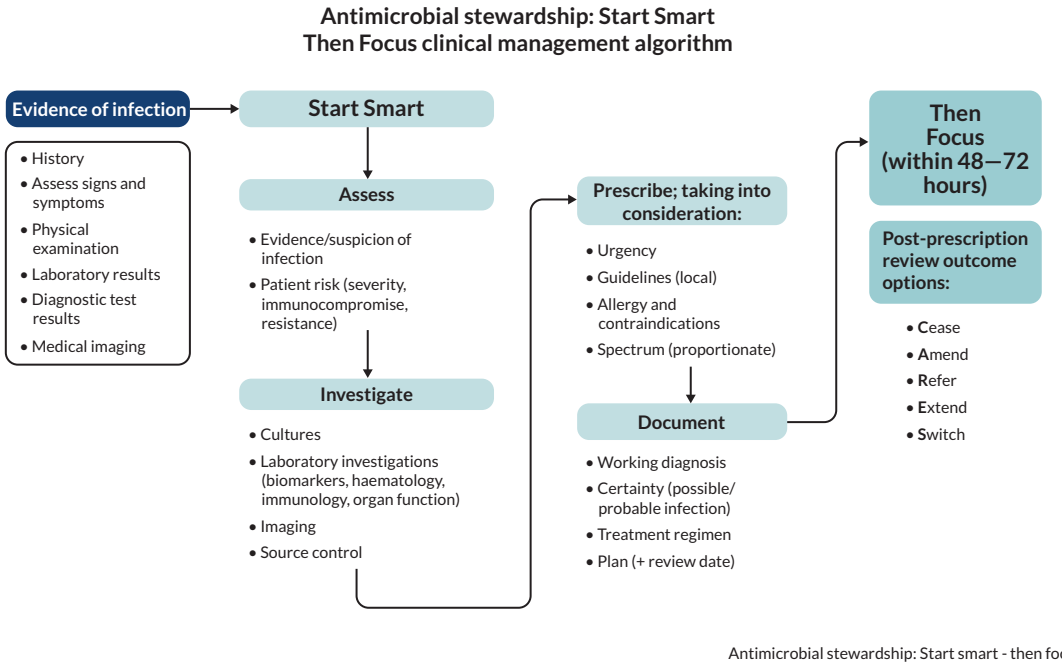

FIGURE 1 Antimicrobial stewardship clinical management algorithm. Reproduced from UK Health Security Agency. Contains public sector information licensed under the Open Government Licence v3.0. See: www.nationalarchives.gov.uk/doc/open-government-licence/version/3/.[10]

and a reduction of resistance rates at a population level have been achieved by the implementation of nationally co-ordinated, whole-system approaches, with no evidence of an increase in the rate of serious infection or bacterial complications.[12] We published a large prospective study assessing the performance of multiple biomarkers of SBI in a heterogeneous cohort of critically ill children and uniquely profiled longitudinal biomarker changes. Longitudinal profiles for PCT showed the greatest percentage drop in values over the first 7 days of therapy in children with SBI, suggesting that PCT might be useful in guiding duration of antimicrobial therapy in children.[13] In conclusion, PCT is a reliable biomarker that (1) changes early in the course of bacterial infection, and (2) correlates with clinical progression to enable real-time monitoring and facilitate clinical decision-making. In critically ill adults with sepsis, PCT kinetics in the first 24 hours after commencing empirical antimicrobial therapy could be used to specifically tailor therapy to PCT response.[14] In this group of patients, dynamic changes in PCT over 48 and 96 hours were predictive of survival.[15]

Procalcitonin testing to guide antibiotic therapy

A systematic review and cost-effectiveness analysis funded by the National Institute for Health and Care Research Health Technology Assessment (NIHR HTA) programme evaluated PCT testing to guide antibiotic therapy for the treatment of sepsis in ICU settings and for suspected bacterial infection in emergency department (ED) settings in adults and children.[16] The review was conducted on behalf of NICE.[7] It concluded that addition of a PCT algorithm to the information used to guide antibiotic treatment may reduce antibiotic exposure in adults in ICU settings and in the ED without any adverse consequences. The use of a PCT algorithm may also be associated with reductions in hospital and ICU stay in adults. For example, the summary effect estimate indicates that the addition of a PCT algorithm to clinical decision-making was associated with a significant reduction in duration of antibiotic therapy [weighted mean difference −1.2 days, 95% confidence interval (CI) −1.33 to −1.07].[16]

In children, very limited data suggested that similar effects may apply for children presenting to the ED with community-acquired pneumonia, but no evidence was identified on the effectiveness of using a PCT algorithm to guide antibiotic treatment for children with suspected or confirmed SBIs admitted from emergency care. None of the identified studies were conducted in the UK, and it was not clear whether the control arms of these studies were representative of standard practice in the UK.

The report recommended further studies to adequately assess the effectiveness of adding PCT algorithms to the information used to guide antibiotic treatment in adults and children with suspected or confirmed SBIs in ICU settings and in adults and children with suspected bacterial infection in ED settings. High-quality studies, in which the control arm is similar to the intervention arm in all respects other than the use of PCT testing, are needed to inform the question of whether any observed effects are attributable to PCT testing or may be due to the effects of introducing protocolised care. It states that further studies are needed particularly for children, where data are currently lacking, and research examining (short-term) health-state utility values in the UK for adults and children with confirmed or suspected SBIs in the ICU and ED.[16]

National Institute for Health and Care Excellence guidance on AMS systems and processes for effective antimicrobial use recommends decision support systems as an AMS intervention.[11] The use of PCT to guide antibiotic stopping or escalation is one such decision support system which can be used. The AMS guidelines made the following research recommendations: (1) RCTs should be undertaken to determine whether short or long courses reduce AMR, and (2) RCTs should be undertaken to determine if using point-of-care tests is clinically and cost-effective when prescribing antimicrobials in children, young people and adults presenting with respiratory tract infections. This study is aligned with these recommendations in seeking to evaluate if PCT-guided management can result in shorter courses of antibiotics. Results presented in this report may help inform recommendations relating to the duration of antibiotic use in future guideline updates including NICE sepsis and AMS guidelines.

A systematic review and meta-analysis of antibiotic duration for bacterial infections in children demonstrated that intravenous (IV)-to-oral switch can occur earlier than previously recommended. The authors produced recommendations for antibiotic duration and IV-to-oral switch to support clinical decision-making and recommend prospective research on optimal antibiotic durations.[17] The lack of good evidence on the recommended duration of antibiotic therapy leads to an overuse of antibiotics, contributing to the development of AMR, a national and global priority. Shorter courses of antibiotic therapy would be associated with reductions in adverse effects for patients and reductions in healthcare resource utilisation.

Results from an observational study of 657 children admitted to paediatric intensive care unit (PICU), with PCT measured longitudinally, suggest that serial measurement of PCT could be used to reduce duration of antibiotic therapy and hospital stay.[13] Differential profiles between children with and without SBI at admission suggest that in many children antibiotics could have been confidently discontinued at 48 hours (in the group with no SBI) or on day 5 (in the group with SBI) using thresholds and percentage reduction in PCT value. This suggests that antibiotics could be stopped at 48 hours if PCT values remain in the normal uninfected range. RCTs in adults, but not children, in ICU have reported on the effectiveness of adding PCT testing to guide antibiotic therapy.

A retrospective propensity score-matched study of adult patients with presumed lower respiratory tract infection (LRTI) reported that patients managed with a PCT-guided algorithm did not have a meaningful reduction in antibiotic duration compared with those who were not tested. The authors conclude that poor implementation of the algorithm may have undermined its effectiveness.[18] A recent review reported that a PCT-guided strategy, when utilised appropriately, can help guide clinicians to individualise and often reduce the duration of antibiotics in patients hospitalized with LRTI or admitted to the ICU.[19] A PCT-guided protocol to stop or de-escalate antibiotics in children after cardiovascular surgery was shown to reduce antibiotic duration without adverse outcomes.[20]

Summary

The BATCH trial aimed to improve AMS in hospitalised children with suspected or confirmed bacterial infection, by reducing antibiotic duration with guidance from an additional PCT biomarker laboratory test.[1] This trial has the potential to impact the clinical care of hospitalised children with confirmed or suspected bacterial infection, which currently accounts for a large proportion of antibiotic use in hospitalised children. This trial is timely as it aligns with the current Department of Health Five Year Strategy and is a response to research recommendations from two published NICE guidance documents (DG18 and NG15).[7,11]

Chapter 2 Methods

Summary of design

The BATCH trial was a pragmatic, multicentre, open-label, parallel two-arm, individually RCT with internal pilot phase, qualitative interview study and health economic evaluations. The trial assessed the use of an additional PCT test in children (aged 72 hours up to 18 years) hospitalised with suspected or confirmed SBI to guide antimicrobial-prescribing decisions. In children randomised to the intervention arm, a PCT test was performed in the hospital laboratory at baseline/randomisation and every 1–3 days while on IV antibiotics. Children in the control arm did not have the PCT test performed. The trial protocol has been previously published.[1]

Objectives

Primary objective

To determine if the addition of PCT testing to current best practice based on the NICE AMS guidelines can safely allow a reduction in duration of IV 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
- unscheduled admissions to PICU with infective diagnosis
- re-admissions to PICU with infective diagnosis
- unscheduled re-admissions with infective diagnosis within a week of stopping IV antibiotics
- recommencing IV antibiotics for the same infection within a week of stopping IV antibiotics
- mortality within 4 weeks.

Secondary objectives

To assess the effect of additional PCT testing to AMS best practice on:

- total duration of oral and IV antibiotics
- time to switch from broad-spectrum to narrow-spectrum antibiotics (defined as per Hagedoorn *et al.*[21])
- time to discharge from hospital
- hospital-acquired infection (HAI)
- suspected adverse drug reactions (ADRs)
- cost of hospital episode
- health-related quality of life (HRQoL).

Also, to provide a detailed understanding of parents' and health professionals' attitudes to, and experiences of, participating in the BATCH trial.

Setting

Participants were recruited from paediatric wards or PICUs within children's hospitals (n = 6) and district general hospitals (n = 9) in the UK.

Site recruitment

The trial was open to participant recruitment from June 2018 and paused briefly between March and May 2020 due to the COVID-19 pandemic. Recruitment was completed in October 2022.

The Clinical Research Network (CRN) in England and the Cardiff and Vale University Health Board Children's Research Unit in Wales supported site recruitment. Clinicians were invited to take part in the trial by CRN e-mail or newsletter. Interested sites were contacted initially by e-mail and asked to provide further information about their feasibility for conducting the trial. This was followed up by telephone from the trial team to discuss the trial in more detail. Each site involved a principal investigator (PI) and research nurse/co-ordinator(s).

Participant selection

The study population included children aged between 72 hours and 18 years admitted to hospital for confirmed or suspected SBI, in whom IV antibiotics were commenced, and who were expected to remain on IV antibiotics for more than 48 hours. Children were randomised once it was clear that IV antibiotics were expected to be prescribed for longer than 48 hours.

Eligibility criteria

Children were eligible to join the trial if they met all the inclusion criteria and did not meet any of the exclusion criteria described in *Table 1*.

Participant recruitment

Identification and screening

Potential participants were identified by the clinical care team, or the clinical members of the research team involved in care of children in the ward, or the general paediatric or infectious diseases (IDs) teams involved in care of children in the ward. This includes a member of the research team visiting the wards where children with confirmed or suspected bacterial infection were admitted to assess eligibility and screening admission lists.

The parents/carers/legal guardians (referred to as 'parents' throughout this report) of children admitted to hospital with suspected or confirmed bacterial infection and commenced on IV antibiotics (or the children themselves if over the age of 16 or under the age of 16 with Gillick competency) were approached by the normal clinical care team and research team and were given a participant information sheet (PIS) about the trial. They were told that their child may be eligible for the trial if IV antibiotics were expected to be continued for more than 48 hours, and they were being given time to think about it, should they be approached later. Approaches and discussions could also be conducted over the telephone to reduce face-to-face contact. Age-appropriate information sheets were provided for children who were old enough to use them.

The clinician or designated research nurse explained the trial to the child's parents and ensured that they had enough time to consider participation and have any questions answered before being asked to sign the consent form.

Eligibility was confirmed by a member of the clinical care team, or delegated members of the research team, who may have been medical or nursing practitioners.

TABLE 1 Eligibility criteria

Inclusion criteria	Exclusion criteria
• All children aged between 72 hours and up to 18 years admitted to hospital for confirmed or suspected bacterial infection, in whom IV antibiotics are commenced, and who are expected to remain on IV antibiotics for more than 48 hours • Conditions including (but not limited to): bacteraemia, central line-associated bloodstream infections, uncomplicated bone and joint infections (such as single-site infection, osteomyelitis with adjacent septic arthritis or septic arthritis with adjacent osteomyelitis), discitis, empyema, pneumonia, pyelonephritis, sinusitis, retropharyngeal abscess, pyomyositis, uncomplicated culture-negative meningitis, intra-abdominal infections, lymphadenitis, cellulitis • First time in the BATCH trial	• Preterm infants age < 37 weeks corrected gestational age, under 72 hours or over 18 years of age • Children admitted moribund and not expected to survive more than 24 hours • Children who had a predicted duration of IV antibiotics of < 48 hours • Children not expected to survive at least 28 days because of a pre-existing condition • Children who had bacterial meningitis,[a] bacterial endocarditis or brain abscess • Children who had complicated bone and joint infections[b] • Children who received antibiotics for surgical prophylaxis • Children who had chronic comorbidities, such as cystic fibrosis, chronic lung disease, bronchiectasis, where there is already a predefined length of course of antibiotics • Children who were severely immunocompromised (e.g. chemotherapy, stem cell transplant, biological therapy for inflammatory or rheumatological conditions) • Children who, in the opinion of the local investigator, were unsuitable for randomisation due to high probability of requiring sustained IV therapy • Children who had a presence of existing directive to withhold life-sustaining treatment • Inborn infants admitted to neonatal intensive care units (NICU), neonatal high dependency units (NHDU), special care baby units (SCBU) or postnatal wards

a Excluded due to NICE guideline on bacterial meningitis having predefined recommendations for duration of IV antibiotics.[22]
b Defined as chronic and/or related to a fracture or fixation device or prosthesis or implant. Chronic osteomyelitis presents 6 or more weeks after bone infection and is characterised by the presence of bone destruction and formation of sequestra.

Note
Patients with paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS) were not considered eligible due to the guidance advising 48 hours of IV antibiotic treatment only.[23]

Informed consent

Informed consent was sought by suitably qualified, experienced and trained personnel in accordance with the good clinical practice (GCP) directive on taking consent and before any trial-related procedures were undertaken. Written informed consent was obtained from the child's parent(s) or the children themselves if over the age of 16 or under the age of 16 with Gillick competency.

The clinician or delegated member of the research team taking consent also assessed the child's capacity to understand the nature of the trial, and where appropriate, the views of children capable of expressing an opinion were taken into account. Children deemed to have sufficient understanding were asked to sign an age-appropriate assent form.

Consent was requested to collect NHS numbers to utilise NHS digital data and store any unused or leftover sample for future research.

Parent(s) were informed that they had the right to withdraw consent from participation in the trial at any time during the trial period, that they had the right to refuse their child's entry to the trial without giving a reason, and that the clinical care of their child would not be affected by declining to participate or withdrawing from the trial.

Only when written informed consent was obtained from the child's parent (or from the child if over 16 years or under the age of 16 with Gillick competency) and they had been enrolled into the trial, were they considered a trial participant. Once consented, participants were allocated a unique trial number [participant identification (PID)], which was the primary identifier for all participants in the trial. Separate informed consent was taken for participation in the qualitative data collection.

Screening logs

All participating sites were asked to keep an anonymous screening log of all ineligible and eligible but not consented/not approached patients. These were used to inform adjustment of recruitment strategies and trial processes and assess potential selection bias.

Registration

Eligible participants who consented to take part in the trial were registered by recording key information, including contact details, past medical and medication history, as well as demographics.

All documentation used for data collection (including outcome measures) were in English as they were designed and validated in English.

Withdrawal

Parents were informed that they had the right to withdraw consent for their child's participation in any aspect of the trial at any time. If parents indicated that they wished to withdraw their child from the trial, they were asked to give a reason for withdrawal.

Declining to participate or withdrawing from the trial did not affect the care of the child. Parents who wished to withdraw their child from the trial were asked to decide whether they wished to withdraw their child from:

- further treatment/trial intervention but participate in all further data collection
- active follow-up but allow existing data and their child's medical records to be used
- sample storage for future studies
- data linkage for future studies
- completing questionnaires
- all aspects of the trial and require all data collected to date to be excluded from analysis.

In all instances for those participants who consented and subsequently withdrew, a withdrawal form was completed on the participant's behalf by the researcher/clinician based on the information provided by the participant's parent(s).

Randomisation and masking

Participants were randomised in a 1 : 1 ratio to receive either current usual standard clinical management (control) or clinical management with the addition of PCT test guidance (intervention). This was typically done between 20 and 48 hours after admission, to fit with the clinical workflow of ward rounds and phlebotomy times for routine blood tests.

Patients were randomised by minimisation, with site and age group as minimisation factors and a random element to reduce predictability and risk of subversion.[24] Participants were randomised remotely using a secure 24-hour web-based randomisation programme controlled centrally by the Centre for Trials Research (CTR) at Cardiff University. Details of the age group cut-offs (0 to 6 months, > 6 months to 2 years, > 2 to 5 years, > 5 years) and random element (80% chance of being randomised to the arm that minimises the imbalance) were documented in a separate randomisation protocol and concealed from the treating teams. Due to the nature of the intervention, participants, people giving the interventions, and those assessing outcomes were unblinded to group assignment, but those analysing the data were masked to group assignment for the analysis of the coprimary outcomes.

Trial interventions

In participants randomised to the intervention arm, a blood sample was sent to the hospital laboratory for a PCT test at baseline/randomisation and every 1–3 days while still on IV antibiotics to align with the clinical workflow and routine laboratory testing where possible. This included instances where IV antibiotics are restarted for the same infection (up to day 28 post randomisation). An additional 1 ml (minimum 0.5 ml) lithium heparin samples were collected for PCT analysis.

The sample flow is shown in *Figure 2*.

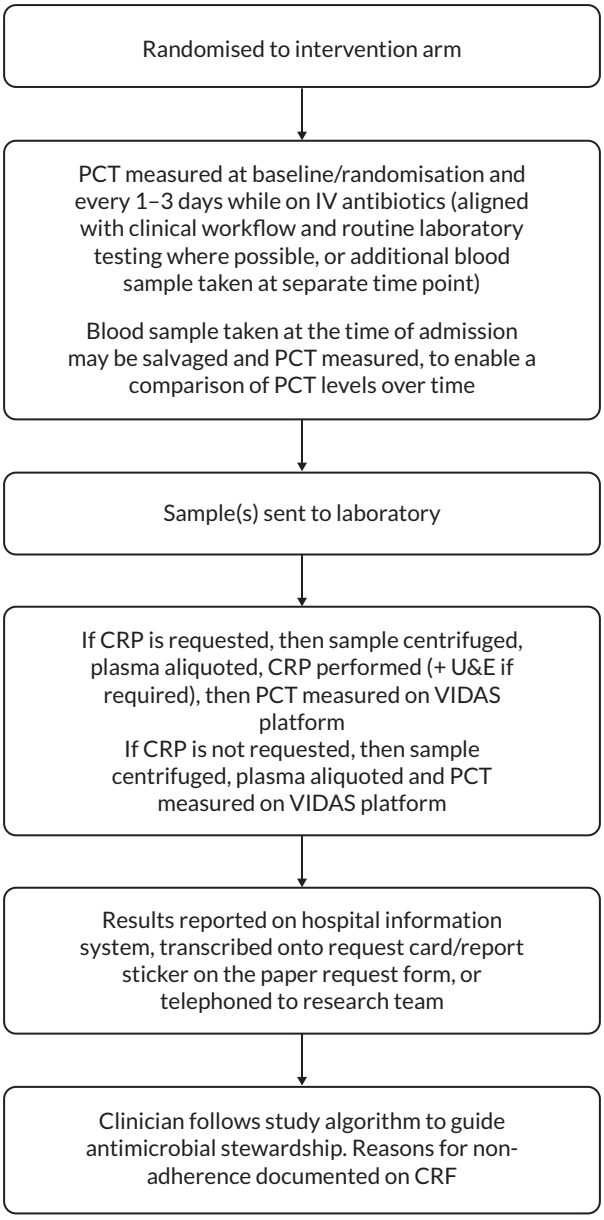

FIGURE 2 Sample flow diagram.

Samples were aimed to be collected at the same time as routine bloods were taken; however, an additional sample may have been needed to be collected at separate time point if routine blood tests were not due, or there was not enough routine blood left over to perform the PCT test.

In addition, for the patients in the intervention arm, if there was no PCT level taken close to randomisation, then the blood sample taken at the time of admission or within the 72 hours preceding recruitment may have been salvaged (these samples are normally discarded after a few days once the routine tests have been performed, so we would have only been using samples that are about to be discarded) and PCT test performed, to enable a comparison of changes in the levels of PCT over time. Surplus blood was stored for future research. Plasma samples were collected and transferred to the sponsor at University of Liverpool for storage.

Procalcitonin tests were performed on a bioMérieux VIDAS platform. It was a prerequisite that participating sites had access to this platform to take part in the trial. This is a semiautomated immunoassay system based on enzyme-linked fluorescent assay principles. Calibration was performed in line with manufacturer's guidelines. It is simple and flexible to

use and gives results in 20 minutes. A quantity of 200 µl of plasma or serum is required and can be run on a sample sent for routine biochemistry after the routine tests have been performed.

PCT results fed into an algorithm (*Figure 3*) that provided both definitive guidelines, for example, stop antibiotics if PCT < 0.25 ng/ml, and advisory guidelines, for example, consider oral switch if PCT decreased by ≥ 80%. The algorithm values were based on now published work which is the largest study to prospectively assess the performance of multiple biomarkers of SBI in a heterogeneous cohort of critically ill children and uniquely profiled longitudinal biomarker changes within the cohort.[13]

Children in the control arm did not have the PCT test performed.

Adherence

Adherence to the algorithm was recorded on the case report form (CRF) and captured instances where the treating clinician overruled the algorithm if they felt it was appropriate to do so.

Trial procedures

All participants were enrolled in the trial from the date of randomisation until day 28 follow-up. *Figure 4* shows the participant flow and trial schema.

Baseline assessments

Once informed consent had been obtained the BATCH research nurse:

- registered the participants and their parent to the trial (this included collecting names and addresses of the participants and their parent)

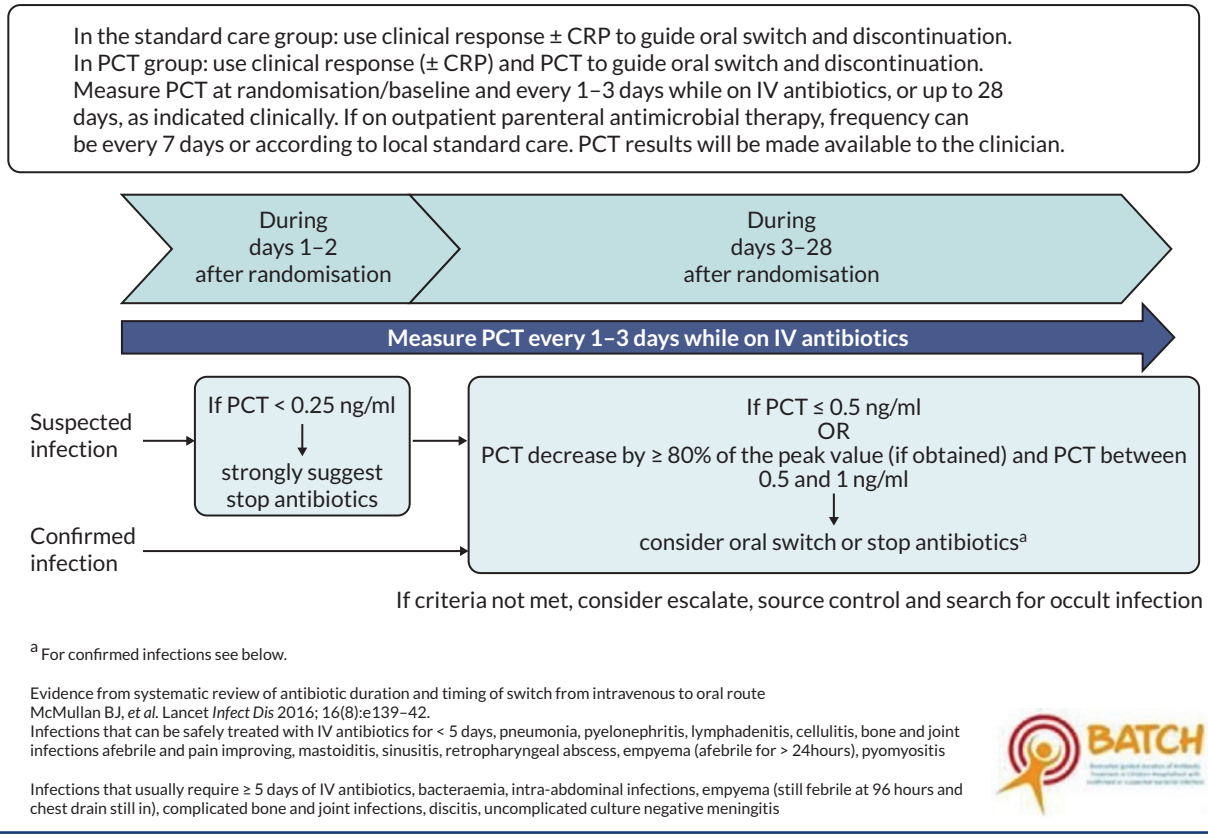

FIGURE 3 Procalcitonin algorithm.

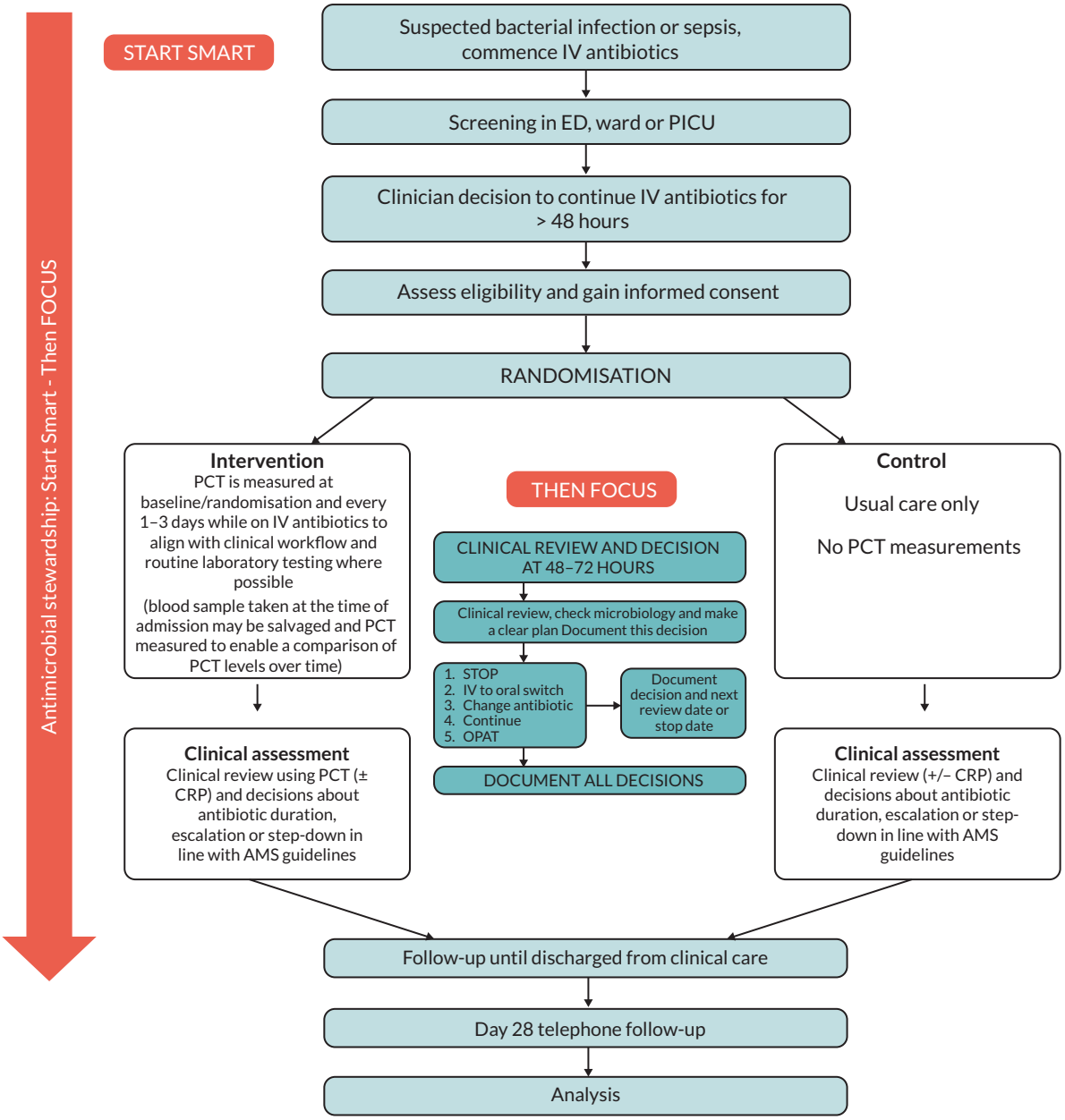

FIGURE 4 Participant flow and trial schema. Based on best practice for antimicrobialprescribing 'Start Smart-Then Focus' Public Health England, March 2015. www.gov.uk/government/publications/antimicrobial-stewardship-startsmart-then-focus. OPAT, Outpatient parenteral antibiotic therapy.

- completed the medical history and baseline CRFs
- provided the HRQoL questionnaires to the parent/legal guardian and completed this with the participant (if appropriate)
- ensure that routine blood sample has adequate quantity for PCT testing or collect a separate sample with the parent's permission (if participant was in the intervention arm).

During hospitalisation

Participants were assessed until they were discharged from clinical care. Outcome data, described in *Table 2*, were recorded daily by the research nurse for all recruited participants (up to and including day 28, or until discharge). Observation and medication charts and medical notes were reviewed. Assessments included antibiotic use, routine test results, PCT measurements and clinician adherence to the algorithm. All clinical management decisions were recorded at all time points.

TABLE 2 Summary of data collection

Data type		Source data	Data type	Screening	Baseline	Post randomisation until discharged home	Follow-up (day 28)	Frequency	By whom
1.	Informed consent	Consent form	–	X				Once	Site clinical/research team
2.	Eligibility assessment	Eligibility CRF	–	X				Once	Site research team
3.	Demographics	CRF			X			Once	Research nurse
4.	Admission data	CRF	Comorbidities, preadmission antibiotic use, initial working diagnosis		X			Once	Research nurse
5.	HRQoL	Questionnaire	CHU9D		X		X	Twice	Patient/parent reported (over telephone or post at day 28)
6.	Randomisation	CRF	–		X			Once	Site research team
7.	Antibiotic use (IV/oral)	Observation charts/medical notes	Antibiotic type, dose, duration			X		Daily	Research nurse
8.	Blood tests including PCT	CRF/medical notes	Routine blood tests PCT results (for those in intervention arm)			X		As required	Research nurse
9.	Clinical review	CRF/medical notes	Clinical decision made and whether the algorithm was complied with			X		As required when a clinical decision has been made	Site clinical/research team
10.	Cerebrospinal fluid metrics, radiology and microbiology	CRF/medical notes	White cell count, biochemistry. Microbiology results, radiology results			X		As required	Research nurse
11.	Recommencing of antibiotics (IV and oral)	Observation charts/medical notes	Antibiotic type, dose, duration, time recommenced			X		Daily	Research nurse
12.	Unscheduled admissions	Medical notes	PICU re-admissions post discharge			X		Daily	Research nurse
13.	Mortality	Medical notes	Date, description			X		If before day 28	Research nurse

continued

TABLE 2 Summary of data collection (*continued*)

Data type		Source data	Data type	Screening	Baseline	Post randomisation until discharged home	Follow-up (day 28)	Frequency	By whom
14.	Discharge	Medical notes	Date, description			X		If before day 28	Research nurse
15.	AEs	Observation charts/medical notes	Date, type			X		Daily	Research nurse
16.	Suspected ADRs	Liverpool Causality Assessment tool	Date, description			X		Daily	Research nurse
17.	Resource use	Questionnaire	Direct medical costs (including medication and ventilation and vasopressor) and resource use				X	Once	Patient/parent reported (over telephone or post)
18.	SAE	SAE form			←----------As required----------→				Research nurse
19.	Withdrawals	Withdrawal form			←----------As required----------→				Research nurse, centre for trial research

For children who were discharged home with outpatient parenteral antimicrobial therapy (OPAT), local procedures were followed. The OPAT nursing team documented the doses received and scanned or sent electronically to the research team. Participants were only identified by their PID number, date of birth and initials only.

Twenty-eight-day follow-up

At day 28 (+ 2-week time window), parents were contacted by telephone or e-mail, and around three to five attempts were made to contact. Patient outcomes (re-admission, retreatment, HAIs, ADRs) and use of healthcare resource [hospital admissions, OPAT, other prescribed medicines, privately purchased over-the-counter medicines, general practitioner (GP) and hospital outpatient attendance] were captured. Furthermore, direct non-medical costs borne by parents and carers as a result of attending hospital with the child (travel costs, child-care costs, expenses incurred while in hospital, self-reported lost earnings and other direct non-medical expenses) were collected.

Health-related quality of life

Health-related quality of life [via Child Health Utility 9D (CHU9D) questionnaire] was assessed at baseline and at the end of the 28-day follow-up period. Parents were asked to support their child to complete the CHU9D questionnaire (where appropriate) and complete the parent proxy version of the CHU9D questionnaire. If efforts to contact them by phone or e-mail were unsuccessful, a questionnaire booklet was posted out with a prepaid envelope for return.

Further description of how these measures were used and interpreted within the economic analysis is given in *Chapter 4*.

Lost to follow-up

It was essential for the trial that every participant complied with the data collection regime. We ensured that data collected could be obtained from the medical notes (where possible). At enrolment, we asked parents of those children recruited to provide contact details for members of the research team to contact while attempting to make follow-up interviews. To minimise loss to follow-up, parents could give permission to be contacted by short message service text messaging. For participants who were unable to be contacted and did not return a paper questionnaire, a partial follow-up from medical notes was done. Participants were considered as lost to follow-up if it was not possible to contact them directly for 6 weeks post randomisation and not possible to collect any data from medical notes.

Safety monitoring

The primary composite safety outcome included instances of the following events, recorded as part of routine data collection, and these therefore did *not* require expedited reporting as serious adverse events (SAEs):

- death
- life-threatening event
- re-admission to hospital or prolongation of hospitalisation.

These adverse events (AEs) instead were recorded in participants' notes and in the relevant CRFs.

The following events were to be reported as SAEs within 24 hours:

- events resulting in persistent or significant disability or incapacity
- congenital anomalies or birth defects.

The following non-serious AEs were also to be recorded as part of routine follow-up at 28 days:

- non-serious AEs potentially attributable to PCT test and step-down approach
- suspected drug reactions defined by the Liverpool Causality Assessment Tool.[25]

These events were recorded in participants' notes and in the relevant CRF.

In the event that a SAE was reported, an assessment of causality between the event and the trial intervention would be carried out by the PI or delegated clinician, and then independently by a clinical reviewer who also assessed expectedness. If the clinical reviewer classified the event as probably or definitely caused by the intervention, it would be classified as a serious adverse reaction.

Other non-serious AEs were not collected.

Protocol deviations

Where protocol deviations occurred, further details were provided (e.g. reasons for non-eligibility). Potential protocol deviations could include:

- participants who were randomised but did not meet eligibility criteria
- participants randomised with incorrect date of birth
- missed/late follow-up assessments
- samples stored at incorrect temperature.

Training

All staff involved in the trial, including clinicians, research nurses/co-ordinators at sites were provided with written standard operating procedures and received trial-specific training in trial procedures and GCP prior to commencing the trial.

Data collection

Participant data were collected at the following time points:

- at baseline (baseline characteristics and admission data)
- daily post randomisation until discharged home (antibiotic use, AEs and clinical data)
- day 28 telephone follow-up (healthcare utilisation and quality-of-life questionnaire).

The schedule for timing, frequency and method of collection of all trial data is summarised in *Table 2*.

Assessments were performed as close as possible to the required time point (e.g. 28 days + 2-week window). CRFs were provided to the appropriate trial staff prior to trial commencement at site initiation. In accordance with the principles of GCP, the PI was responsible for ensuring accuracy, completeness, legibility and timeliness of the data reported in the CRFs.

Source data were from a variety of sources including patient's medical notes and patient-reported questionnaires. Data were collected using an electronic system, encrypted and accessed by individual username and password. If the electronic database was not available, paper copies of the CRFs were used and data were entered on to the database retrospectively.

Data management and monitoring

Data management

Data received from participating study sites were checked for missing, illegible or unusual values (range checks) and consistency over time. Details of data management procedures were specified in the BATCH Data Management Plan.

Data monitoring

Data monitoring was conducted throughout the trial across all recruiting sites; this included a 10% quality control of all data sets. Further monitoring was triggered if an error rate > 1% was detected. Details of monitoring procedures were specified in the BATCH Monitoring Plan.

Data cleaning

The database was built with internal validations and ranges; queries arising during data entry were referred back to the site research nurses. Where data collected on paper CRFs conflicted with that collected via the web-based database, the value on the paper CRF was deemed the true value unless the paper CRF had already been appropriately annotated with a correction. Self-evident correction rules were developed during the course of the trial, in response to common errors of CRF completion.

Data queries for any identified missing or questionable data were raised on a data clarification form that was sent to the appropriate site. The delegated member of staff at the site responded to the data query and completed data clarification form. All data queries and corrections were signed off and dated. The CRF pages were not altered. The completed data clarification form was returned to the CTR, and a copy retained at the site along with the participants' CRFs. It was the site's responsibility to submit complete and accurate data in timely manner. The CTR sent reminders for any overdue data.

Research governance

This trial had ethical approval granted by an NHS Research Ethics Committee (REC), recognised by the United Kingdom Ethics Committee Authority (UKECA). The initial approval was granted by the North West Liverpool East REC on 12 April 2018, reference number 18/NW/0100. NHS Research and Development (R&D) confirmation of capacity and capability was sought from the respective NHS relevant organisations in Wales and England.

The trial was assigned the International Standard Randomised Controlled Trial Number (ISRCTN) ISRCTN11369832 (registered 20 September 2017).

Patient and public involvement

Patient and public involvement (PPI) was incorporated into design and conduct throughout the research process, from conceptualisation to dissemination. An example of this was the active involvement of the Liverpool GenerationR Young People's Advisory Group (YPAG) in contributing to the design of this research.[26] The group consisted of 24 young people aged between 8 and 21 years who have worked with several researchers exploring the topic of developing tests to rapidly detect or diagnose SBI in children, including the development of a rapid salivary test to detect SBI in children presenting to the ED (SPICED study), and a study looking at the diagnostic biomarkers in children on PICU (DISTINCTIVE study). The Liverpool GenerationR YPAG members were well aware of the problems associated with diagnosing and treating SBIs 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.

The Liverpool GenerationR YPAG were involved throughout the duration of the trial and reviewed the children's information sheets and the production of educational materials for young people and families on the most appropriate use of antibiotics. They partnered with Antibiotic Action, a charity promoting public awareness about antibiotics and AMR, and utilised their resources. They were 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. They also coproduced a youth led drama project to raise awareness of antibiotic resistance with children, families and healthcare professionals (HCPs) (see *Chapter 8*).

Parent representatives joined the Trial Management Group (TMG), Trial Steering Committee (TSC) and Independent Data Monitoring Committee (IDMC). Members of the YPAG and parents were trained by our PPI lead. The parent representatives have contributed throughout the course of the trial and will continue to provide input into dissemination activities, for example, we will invite parents and young people to actively contribute to dissemination events, including presenting parents' and young peoples' views and stories.

Internal pilot

An internal pilot phase was conducted over the first 8 months of the recruitment period with six lead sites. Predefined progression criteria were used to assess feasibility to progress to the full trial, such as site and patient absolute recruitment and consent rates, proportion of participants undergoing PCT assessments and the ability to collect primary outcome data. The progression criteria were designed to allow for mitigating strategies to be discussed to allow for some adaptation to recruitment processes.

We constantly assessed the criteria during the internal pilot phase. We also conducted a qualitative evaluation of the acceptability of the algorithm with clinicians and identified any problems with contamination/changes to usual care (UC) in the control arm (see *Chapter 2, Site observation* below). Feedback from these interviews fed into the progression criterion in terms of considering contamination during the pilot phase.

To progress from the internal pilot phase to the full trial, we utilised the following criteria in *Table 3*.

TABLE 3 Progression criteria

Criteria	Level	Action
Absolute number of recruited patients[a]	> 350	GO
	200–350	Discuss potential mitigating strategies
	< 200	STOP
Eligible patients identified	> 50%	GO
	> 30%, < 50%	Discuss potential mitigating strategies
	< 30%	STOP
Consent rate	> 50%	GO
	30–50%	Discuss potential mitigating strategies
	< 30%	STOP
Consideration of the PCT result and algorithm during clinical decision-making at each PCT test (in intervention group)	> 60%	GO
	40–60%	Discuss potential mitigating strategies
	< 40%	STOP
Contamination/changes to UC in control arm	Qualitative interviews	
Ability to collect primary outcome information	> 90%	GO
	80–90%	Discuss potential mitigating strategies
	< 80%	STOP
Ability to collect day 28 follow-up information	> 75%	GO
	60–75%	Discuss potential mitigating strategies
	< 60%	STOP

a Included all participants recruited during pilot.

Outcome measures

Primary outcome measure

The trial used a coprimary outcome of antibiotic use and safety (*Table 4*).

- Duration of IV antibiotic use was measured in hours.
- Safety was defined as the absence of all of the following:
  - Unscheduled admissions/re-admissions (to include re-admission within 7 days of discharge with infective diagnosis, unscheduled re-admission to PICU with infective diagnosis or admission to PICU with infective diagnosis).
  - Retreatment for same condition within 7 days of stopping IV antibiotics (restarting IV antibiotics which have been stopped).
  - Death for any reason in the 28 days following randomisation.

Secondary outcome measures

- Total duration of antibiotic use (IV and oral).
- Duration of broad-spectrum antibiotic use.
- Time to discharge from hospital.
- Suspected ADR (yes or no).
- Cost of hospital episode.
- HAI as defined by the clinical team up to day 28.
- Health utility as measured by the CHU9D[30] up to day 28.
- To provide detailed understanding of parent and health professionals' attitudes to, and experiences of, participating in the BATCH RCT.

Sample size

Two coprimary outcomes (IV antibiotics duration and a composite safety outcome) were defined in this trial[31] and the overall sample size was determined by both.

The focus for the intervention was moving the step down from IV to oral therapy earlier, and therefore the time until this step down was the primary outcome on antibiotic usage, and the trial was powered to detect if PCT-directed care is *superior* to standard care on time until switch from IV antibiotics. The size of potential shortening of time to detect an effect has been taken from a systematic review.[16] The safety coprimary was a composite measure reflecting various outcomes which represented deterioration or lack of clinical response in the child, and would be expected to increase if IV antibiotics were being withdrawn inappropriately early.

TABLE 4 Elements of the composite safety outcome

Composite element	Definition	Reason for inclusion	Expected prevalence in UC	Potential direction of change with intervention
Unscheduled admissions/ re-admissions	Admitted/re-admitted to PICU or unplanned re-admission to hospital within 7 days of stopping IV antibiotics	Indicators of a deterioration and need for increased level of care	Our observation study showed that 8.8% patients have admissions/re-admissions[27]	Increase
Reinstating IV antibiotic therapy	Restarting IV antibiotic (for any reason) therapy within 7 days of stopping IV therapy	Indicator of potentially inappropriate withdrawal of IV antibiotics and deterioration	de Jong *et al.* study 2.9% in control arm restarted IV antibiotic[28]	Increase
Mortality	Death for any reason in the 28 days following randomisation	–	PICA Net Annual report 2015: deaths in PICUs ~ 4% in 2012–4[29]	Increase

In terms of IV antibiotic duration, a 1-day reduction[29] in antibiotics from an estimated median of 5 days in the control arm (from our observation data[27]) demonstrated a hazard ratio (HR) of 1.25. At a 5% significance level with 90% power, and based on a log-rank test, 844 participants with observed IV antibiotics duration were needed. In terms of the event rates of safety elements, an observational study showed a re-admission rate of 15% at day 28.[32] In critically ill patients, up to 3% reinstating IV antibiotic therapy rate and 4% mortality were reported.[16,29,33] With some overlaps considered, we estimated around 15% overall rate of our composite safety outcome. The Stop Antibiotics on Guidance of PCT trial in adults used a non-inferiority margin of 8% for mortality.[16] Given the lower expected rate of safety outcomes in this population, we chose a similar relative non-inferiority bound of 5%. This means increases in the composite safety measure of < 5% (from 15% to 20%) using PCT-guided therapy would be considered as not inferior. With a one-sided significance level of 5% and 90% power, we needed 1748 participants to test non-inferiority. Overall, with 1748 effectively recruited participants, we had 99% power to detect antibiotic duration decrease and 90% power to test non-inferiority in safety separately. Assuming that these two coprimary outcomes are independent, this gave us at least 89% power for the combined analysis.[34] As no multiplicity correction was deemed necessary for the analysis, no further adjustment of the sample size due to multiplicity was undertaken. By considering 10% loss to follow-up for the primary outcomes, our final targeted sample size was inflated to 1942.

Analysis

A comprehensive statistical analysis plan was finalised and published prior to any data being analysed.[35]

Post hoc derivation of the primary and secondary duration

Detail on the post hoc derivation of the primary and secondary duration outcomes is shown is *Appendix 1*.

Definition of non-adherence

There were multiple measures of non-adherence, which reflected different stages of the clinical decision-making. Reasons for non-consideration of the PCT result or non-adherence to the algorithm were broken down into three steps (*Table 5*). A patient may have had multiple clinical reviews, so all three adherence steps were recorded at each clinical review. In cases where the PCT result was available and was considered, this was considered adherence to the intervention policy specified in the trial protocol, regardless of the actual clinical decision.[1]

In this clinical context, contamination of the control arm was very unlikely, that is we did not expect that any patient in the control arm would have a PCT test done.

Analysis populations

All randomised patients remained in their originally assigned groups, regardless of protocol deviations or non-adherence, and were included in all analyses if outcome data were available.

In one of the planned secondary analyses, we estimated the complier-average causal effect (CACE)[36] to account for departures from the randomised intervention. For the purposes of this sensitivity analysis, we defined adherence using the three steps described in *Table 5*.

TABLE 5 Types of non-adherence

Non-adherence step	Reasons or examples
1. PCT results not available	Blood samples not obtained, loss of IV access, blood sample insufficient for laboratory analysis, PCT machine issues, or results not available for ward rounds
2. PCT results not considered	If a PCT result was available, protocol required that it be considered as part of clinical decision-making
3. PCT algorithm not adhered to	If the PCT result was considered, protocol does not require clinicians to follow the PCT-guided algorithm. Clinical judgement may override the PCT-guided algorithm. Therefore, non-adherence to the PCT-guided algorithm is consistent with adherence to intervention policy

Reporting

Final analysis of the primary and secondary outcomes took place when all randomised patients had completed their day 28 telephone follow-up, all forms had been received, and the data sets had been locked. The trial report followed the guidelines of Consolidated Standards of Reporting Trials (CONSORT) for reporting RCTs[37] and its extension to non-inferiority designs.[38]

Statistical principles

Levels of confidence

To assess non-inferiority of the composite safety outcome, a one-sided 95% CI was calculated. Other outcomes were assessed using two-sided 95% CIs. Hypothesis tests were conducted with Type I error rate of 5%.

Multiple testing

The trial had two arms, and no interim analyses were conducted. The coprimary outcome was assessed as an intersection–union test,[34] meaning that we considered the intervention successful if and only if both components were successful, that is if it concluded both non-inferiority of the composite safety outcome and also superiority in terms of providing lessons learnt for future trials with children in intensive care settings of IV antibiotic duration. No adjustment for multiplicity was therefore necessary for the coprimary outcome. We had planned to correct for multiple hypothesis testing among the secondary and subgroup analyses by controlling the false discovery rate at 5%.[39] This was not done, however, since every result was non-significant even without multiplicity adjustment.

Distributional assumptions

Modelling and distributional assumptions were checked prior to reporting. Specifically, time-to-event models were tested for the proportional hazard (PH) assumption, and logistic regression models were assessed for overdispersion.

Statistical software

Stata version 17[38] (StataCorp, Stata Statistical Software: Release 17, College Station, TX, USA: StataCorp LLC; 2021) was used for statistical analysis and R version 4.3.1[39] (R Core Team, R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria; 2022) for data cleaning, reporting and visualisation of results.

Statistical analyses

Descriptive analyses

Screening, eligibility, recruitment, withdrawal and loss to follow-up

Summary statistics on screening, eligibility, recruitment, withdrawal and loss to follow-up were reported in the CONSORT diagram (*Figure 5*).

Safety reporting

No SAEs or AEs that met the definitions described above (see section *Safety monitoring*) were recorded, therefore no analyses were performed.

Baseline characteristics

Participant characteristics were reported as frequencies and percentages, means and standard deviations, or medians and interquartile ranges (IQRs), as appropriate. Baseline characteristics were reported by trial arm for all randomised patients. There was no statistical comparison (e.g. using hypothesis tests) of baseline characteristics.

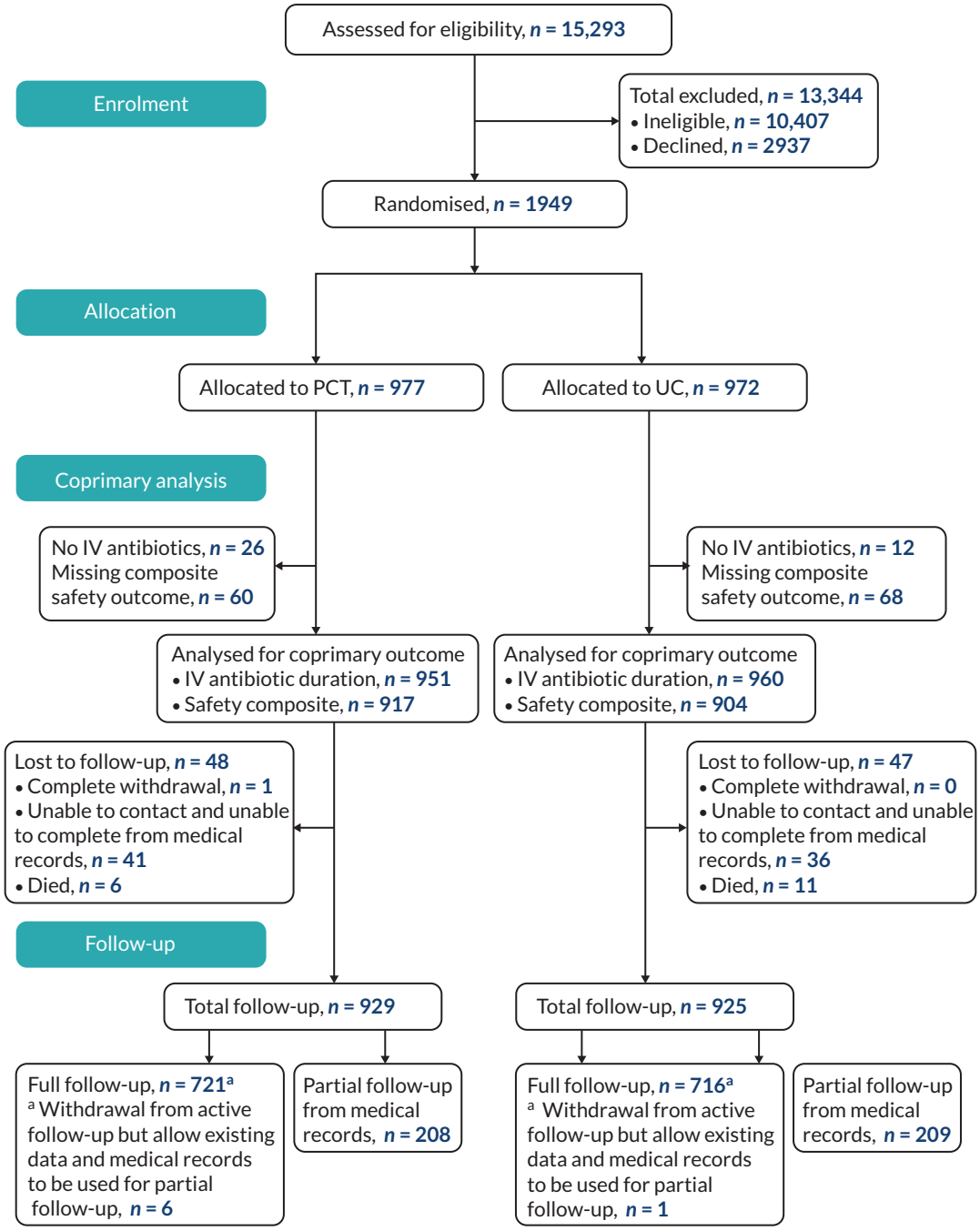

FIGURE 5 The BATCH CONSORT diagram.

Primary outcome

The trial had two coprimary outcomes[31] which were combined using the criteria specified in *Table 6*. We compared the duration of IV antibiotic treatment between arms using Cox regression. We used logistic regression to construct a one-sided CI for the risk difference (RD) of the composite safety outcome via the delta method.[40] Non-inferiority was concluded if the upper bound of the CI was below + 5% on the RD scale. Trial arm and the minimisation factors were included as covariates in both models, with centre as a random effect and age as a fixed effect. The intervention was judged successful if and only if it was found to be both superior with respect to IV antibiotic duration and non-inferior with respect to the composite safety outcome (see *Table 6*).

A summary of the analyses of the coprimary outcomes is given in *Table 7*.

TABLE 6 Combined primary outcome

	Antibiotic duration different (H1)	Antibiotic duration not different (H0)
Safety composite not worse in PCT group (H1)	✓	✕
Safety composite worse in PCT group (H0)	✕✕	✕✕

✓, intervention successful if antibiotic duration is reduced in PCT group; ✕, intervention unsuccessful; ✕✕, intervention harmful.

TABLE 7 Summary of analyses of coprimary outcomes

	Coprimary outcomes	Analysis approach	Covariates in the model
Primary analysis	Duration of IV antibiotics (intervention effect)	Cox regression (superiority)	Trial arm and minimisation factors (site, age)
	Composite safety outcome	Logistic regression (non-inferiority)	Trial arm and minimisation factors (site, age)
Secondary analyses	Duration of IV antibiotics (intervention effect)	Kaplan–Meier plot	Trial arm
		Log-rank test	Trial arm
		CACE	Covariates in the primary analysis, plus intervention adherence
	Composite safety outcome	CACE	Trial arm, minimisation factors, and intervention adherence

Secondary outcomes

For secondary outcomes, differences in the proportion of ADR, HAI, unscheduled re-admission, recommencing IV antibiotics and 28-day mortality were assessed separately by logistic regression models. We assessed differences in the total duration of antibiotics (IV and oral), duration of broad-spectrum antibiotics and time to discharge from hospital using Cox regression (*Table 8*). Ineligible participants were excluded in a sensitivity analysis.

Subgroup analysis

We performed subgroup analyses on the primary outcomes based on pre-specified baseline characteristics: by infected organ system and recruitment before/after the COVID-19 pause (planned) and by recent surgery and whether the recruiting site had an AMS programme in place (post hoc). The trial was not powered to reliably detect subgroup effects. Subgroup findings were considered exploratory and did not affect the trial's main conclusions.

In each subgroup analysis, we investigated how the treatment effect varied between subgroups by adding the grouping variable as a covariate in the main analysis model, both with and without a treatment-arm interaction term. The models with and without the interaction were compared using a likelihood-ratio test (LRT). We reported the LRT χ^2 statistic and illustrated the direction of the subgroup effect (if any) using interaction plots.

Sensitivity analyses

The sample size calculation assumed a 15% rate of the composite safety outcome in the control group. Because the non-inferiority margin was defined using a fixed RD, deviations from the assumed control group rate could cause a reduction in power (if > 15%) or an inflation of the tolerable relative risk in the treatment group (if < 15%). We therefore repeated the primary analysis with the non-inferiority margin modified according to the power-stabilising arcsine transformation.[41] If the observed rate in the control group was < 15%, we also assessed non-inferiority on the relative risk scale: the risk ratio (RR) was calculated via the delta method,[40] and non-inferiority was concluded if the upper bound of the CI was below 4/3. When the control group rate was < 15%, this relative non-inferiority margin was more stringent than the absolute margin used in the primary analysis.

TABLE 8 Summary of analyses of secondary outcomes

Secondary outcomes	Analysis approach	Covariates in the model
Proportion of ADR	Logistic regression	Trial arm and minimisation factors (site, age)
Proportion of HAI		
Proportion of unscheduled re-admission		
Proportion of recommencing IV antibiotics		
Proportion of mortality		
Duration of antibiotics (IV and oral)	Cox regression	Trial arm and minimisation factors (site, age)
Duration of broad-spectrum antibiotics		
Time to discharge from hospital		

We used CACE[36] derived in a two-stage regression and with bootstrapped CIs to account for departures from the randomised intervention. CACE estimates the intervention effect for the subset of patients who received fully compliant treatment in either trial arm. If patients were recruited but subsequently found to be ineligible, we performed an additional sensitivity analysis which excluded all ineligible patients.

We had planned to use survivor average causal effects (SACE)[42] to account for the fact that IV antibiotic duration is undefined for patients who died before IV antibiotics were stopped. SACE would have estimated the intervention effect for the subset of patients who would have survived under either treatment. This analysis was not conducted due to the very small number of participants who died while on IV antibiotics.

To assess the impact of missing composite safety outcome data, we compared the results of the primary analysis (complete cases) with estimates from two simple imputation models. We assumed that all missing values in the PCT arm were safety events and all missing values in the UC arm were not ('worst case'), or vice versa ('best case'), providing upper and lower bounds for the treatment effect on the composite safety outcome.

Missing, unused and spurious data

Complete-case analysis was used for the primary analysis. Missingness (frequency and percentage) was reported for each combination of the components of the composite safety outcome. For the primary analysis, the composite safety outcome was considered missing if (1) data on unscheduled re-admission was missing and (2) the patient was not known to have experienced at least one of the two other components. This assumed that it would be known if a patient had restarted IV antibiotics or died. The potential influence of this assumption was investigated by comparing estimates from best-case and worst-case imputation.

Missing data on IV antibiotic-stopping time led to censoring at the participant's last available clinical review. Participants with missing outcome data could therefore still be included in the Cox regression model, under the assumption that this censoring was non-informative.

Health economics

Health economic analysis included direct and indirect costs associated with unscheduled admissions (to ward or PICU), re-admissions, restarting IV antibiotics and HAIs. Descriptive and regression analysis was used to identify key elements of service use and cost and explored the potential impact of baseline patient characteristics on the costs and outcomes measures. Average cost per patient was estimated at the end of the treatment and the follow-up periods, respectively, and average cost per subgroup of patients was explored for the same time points. Bootstrapping and missing data imputation were done if justified. Differences in each arm were assessed and used for the computation of

an incremental cost-effectiveness ratio (ICER). We calculated ICERs for a clinically effective outcome (fewer days on IV antibiotics with increased or equivalent safety) and the cost per IV antibiotic day avoided.

A cost-effectiveness analysis assessed possible efficiency gains. An NHS perspective was used, and relevant direct medical costs were collected. Information on resource used included data on inpatient bed-days, antibiotic consumption, nursing and medical resources, other medicines including over-the-counter medicines, diagnostic and monitoring laboratory tests, GP visits and emergency visits. Direct hospital costs were calculated by multiplying resource use with the accompanying unit costs collected from patient-level data in the participating hospitals, routine NHS sources, for example, NHS reference costs and *British National Formulary* (BNF) and from the manufacturer of the PCT test, as appropriate. Time horizon was 28 days, therefore there was no need to consider a discount rate. Patients' health utility was measured using CHU9D up to day 28.

Descriptive and regression analysis was used to identify key elements of service use and cost and to explore the potential impact of baseline patient characteristics on the costs and outcomes measures. Differences in each arm were assessed and used for the computation of an ICER. A cost-effectiveness plane was constructed. Information on direct non-medical costs, such as travelling to and from the hospitals, and indirect costs, such as parents' productivity losses, was also collected.

In a subsample of children, we used time–motion techniques to measure the additional parental time, resource use and costs incurred during the child's hospital stay.

More detail on the health economic analysis is described in *Chapter 4*.

Qualitative

Qualitative process evaluation

We carried out a qualitative process evaluation to understand mechanisms of impact and contextual factors that affect how the trial and the intervention were implemented and received by patients.[43] This can provide an insight into why an intervention fails or, if it is successful, how it can be optimised.[44] Qualitative methods are particularly important when a trial is to be undertaken with a complex patient group or within a complex environment.[45]

More specifically, this qualitative evaluation aimed:

1. to explore the experiences and understanding of parents of children in the trial about their child's condition and treatment of confirmed or suspected bacterial infection
2. to explore the experiences and views of parents of children in the trial about the intervention (including acceptability of intervention) and about participating in a RCT (including consenting, trial information and randomisation) and influences on these factors
3. to explore the experiences and views of health professionals involved in the trial about the intervention (including acceptability of the intervention, how delivery of the intervention was achieved, and how the intervention components and delivery processes worked in the real healthcare setting) and about participating in a RCT (including acceptability of the trial, clinical equipoise, taking informed consent).

Semistructured interviews

We used semistructured qualitative interviews to encourage participants to initiate and elaborate on topics most important to them which we may not have pre-empted if using survey-type closed questions. Semistructured interviews were conducted with HCPs and parents. Parent interviews were undertaken via telephone, and professional interviews were a combination of face to face and telephone. The length of the interviews varied but were expected to take about 30–60 minutes.

Topic guide

Semistructured interview topic guides were developed with input from the multidisciplinary research team to avoid bias in wording of questions. The topic guides were refined as necessary. The direction of questions could be led by the participants themselves, and therefore the interview topic guide remained flexible, in keeping with the method of semistructured interviewing.

Parent interviews

The qualitative study aimed to explore the experiences and understanding of parents of children recruited into the trial (*n* = 10–15) about their child's condition and treatment of confirmed or suspected bacterial infection, and also to explore their views and experiences about participating in a RCT. Interviews were conducted after the participant reached their day 28 follow-up (with sensitivity shown to the child patient's current state of health).

Sample size was based on guidance on using qualitative methods within feasibility studies for trials.[45] A purposive sample of parents of child patients' participating in the trial was identified. We anticipated that a sample size of 10–15 parents would be sufficient. Additional parent interviews were carried out focusing on comorbidity aspects, where appropriate. The sample strategy was developed to include parents from both the intervention and control arm, and inclusion of different sites. By sampling in this way, we envisaged there would be a range in terms of child age and gender, parent age and gender, carer role (i.e. mother, father, etc.), range and severity of child patient condition, to ensure maximum variation.

The interviews took place at a time convenient to the parent over the telephone. For telephone interviews, if written informed consent could not be obtained in person before the interview, consent was taken verbally (i.e. statements on the consent form were read out and the participants were asked to verbally confirm their agreement with the statements before the interview commenced).

Healthcare professional interviews

The qualitative study also aimed to explore the views and experiences of HCPs involved in the trial (*n* = 10–20) about participating in a RCT, with a focus on acceptability of the trial, clinical equipoise, taking informed consent, and support needs of trial involvement. Interviews were conducted at two time points (at the beginning or earlier in the trial, and later in the trial) to enable us to capture whether there are any changes in attitudes towards the PCT test: interview 1 explored initial perceptions of possible facilitators and barriers to the test; interview 2 explored actual experiences of using the intervention once the process had been better established and reflections back across the whole trial process.

A purposive sample strategy was developed to address representation from at least five different sites and variation in health professional role (ward nurse, consultant, research nurse, etc.) These semistructured interviews were undertaken face to face or via telephone.

We anticipated that interviews with around 10–20 HCPs based on saturation and breadth of views expressed would be sufficient. Additional staff interviews were carried out focusing on comorbidity aspects.

With regards to the sample size for both parents and HCPs, the qualitative researcher(s) made pragmatic decisions along with the research team regarding when enough was known about certain themes (i.e. data saturation had occurred).

Site observation

To inform the pilot phase, observation of trial delivery was carried out in three centres. The observations and interviews of trained qualitative researchers enabled us to understand how the intervention and delivery processes worked in the real healthcare setting, and the complex environment in which consent must be taken. The qualitative researcher(s) worked with the trial team and trial deliverers at individual sites and developed a detailed non-participant observation strategy. This included the unit of observation (the people to be observed, e.g. research nurse, consultant) and the observation period.

Qualitative study data management

Interviews were audio-recorded and transcribed verbatim. Recordings were not labelled with the participant's name. References to identifiable personal details were removed from the transcript. Information, including any personal information (e.g. participant name, address, date of birth), was kept completely confidential and does not appear in any publications or reports. Written quotes of what the participant said in the interview may have been used word for word, but quotes were de-identified. Details of data management were specified in the BATCH Data Management Plan.

Qualitative analysis

Qualitative coding software, NVivo[45] (NVivo Qualitative Data and Analysis Software, QSR International, Warrington, UK; 2018) was used to manage the data. A thematic coding framework was developed and refined by an experienced qualitative researcher (LBH).

Data were analysed using thematic analysis and drew on the principles of qualitative framework analysis.[46] The framework approach involved a systematic five-stage method (including familiarisation; developing a thematic framework from the interview questions as well as emerging themes; indexing; charting; and mapping) which is increasingly being used in healthcare research.[47] The method is well defined and allows for greater transparency. We identified points of contrast as well as similarities.

Measures were put into place to enhance validity and reliability. More than one qualitative researcher was involved in data collection and analysis, and double coding was carried out to allow for greater reflection and discussion around themes.

Summary of changes to the trial

Previous eligibility criteria were:

All children up to 18 years old admitted to hospital for confirmed or suspected SBI, in whom IV antibiotics are commenced, and who are expected to remain on IV antibiotics for at least 48 hours.

This was changed to exclude infants ≤ 72 hours[48–51] as there are several reports that PCT values in healthy term neonates show broad variation in the first 24–48 hours of life, unrelated to infection.[49,50,52–56]

Previous exclusion criteria were:

- preterm infant age < 37 weeks corrected gestational age, under 72 hours or ≥ 18 years of age
- children admitted moribund and not expected to survive more than 24 hours
- children with a predicted duration of IV antibiotics of < 48 hours
- children not expected to survive at least 28 days because of pre-existing condition
- bacterial meningitis, bacterial endocarditis, brain abscess
- children receiving antibiotics for surgical prophylaxis
- chronic comorbidities, such as cystic fibrosis, chronic lung disease, bronchiectasis, where there is already a predefined length of course of antibiotics
- severely immunocompromised (e.g. chemotherapy, stem cell transplant, biological therapy for inflammatory or rheumatological conditions)
- children, who in the opinion of the local investigator, are unsuitable for randomisation due to high probability of requiring long-term IV therapy
- presence of existing directive to withhold life-sustaining treatment.

Complicated bone and joint infections were added as an exclusion following discussion by the TMG that these children would normally receive prolonged courses of IV antibiotics, and a PCT result would not likely influence that decision.

Comorbidities where there is already a predefined length of course of antibiotics were added as an exclusion following discussion by the TMG that these children would normally receive a defined length prolonged courses of IV antibiotics, and a PCT result would not likely influence that decision.

Inborn infants admitted to NICU, NHDU, SCBU or postnatal wards were also added as an exclusion.

Minor changes to the planned trial procedures with regards sample collection included:

- inclusion of blood samples taken at a separate time point to routine blood samples if needed (i.e. if routine bloods were not due or there would not be enough left over after routine tests had been done)
- inclusion of samples that were salvaged from the point of admission in the preceding 72 hours prior to recruitment, to cover weekends, to enable a better comparison of PCT levels
- continuation of PCT tests if IV antibiotics are restarted for the same infection up to day 28.

Protocol amendments due to COVID-19 included:

- clarification that paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS) should not be included due to shorter duration of antibiotics
- amendment to PID and recruitment procedures where approaches and discussions could be conducted over the telephone to reduce face-to-face contact, and local NHS Trust/Health Board procedures to be followed regarding obtaining copies of the consent form if the patient had confirmed or suspected COVID-19 or had been using a continuous positive airway pressure machine.

Chapter 3 Quantitative results

Internal pilot

The IDMC and TSC reviewed the trial internal pilot findings against the STOP/GO progression criteria (see *Table 3*) in January and February 2019 retrospectively. They were supportive of continuing the trial. No 'red' stopping criteria were met, and where an 'amber' criterion was met, both committees were satisfied with the mitigating strategies proposed by the trial team, such as improving recruitment rates and increasing the number of sites, and they also made their own recommendations, such as proposing an extension to the recruitment period and bringing site PIs together to discuss best practice.

Site recruitment

A total of 15 sites were initiated and opened to recruitment, an additional 3 sites started the R&D review process but were not able to confirm capacity and capability.

Recruitment was open between 11 June 2018 and 12 October 2022, with an enforced pause in 2020 due to the COVID-19 pandemic. The follow-up period ended on 20 January 2023. Of the 15 sites, 8 closed to recruitment early due to either poor recruitment, data-quality concerns or lack of capacity after the pandemic.

Participant recruitment

A total of 15,282 children were screened for eligibility. A total of 10,509 reasons for exclusion were given for 10,407 children (due to there being multiple reasons for exclusion for some children). The main reasons for exclusion were predicted duration of IV antibiotics < 48 hours (*n* = 6279, 59.7%), antibiotics received for surgical prophylaxis (*n* = 1055, 10.1%), and being severely immunocompromised, for example, chemotherapy, stem cell transplant, biological therapy for inflammatory or rheumatological conditions (*n* = 851, 8.1%). A total of 2916 were unable to be approached or consented at site or the parents declined to participate. The most common reasons were due to antibiotics being changed or stopped before consenting (*n* = 357, 12.2%), safeguarding or social issues (*n* = 275, 9.4%) and language barrier (*n* = 265, 9.1%). The parents of 536 (18.4%) children declined participation without giving a reason, 80 (2.7%) declined as they stated they were too stressed/anxious to consider the trial, had too much going on or it was not a good time, and 75 (2.6%) did not want any additional blood taken or extra blood tests being carried out.

In total, 1949 participants were recruited. Of these (*n* = 1703), 87.4% were recruited by the six lead children's hospital sites (Alder Hey Children's Hospital, Bristol Royal Hospital for Children, Southampton Children's Hospital, Oxford Children's Hospital, Sheffield Children's Hospital and Noah's Ark Children's Hospital for Wales). A total of 977 were randomised to receive PCT-guided antibiotic therapy and 972 to UC. The primary intention-to-treat analysis of the coprimary endpoints was conducted on 1911 patients with available non-zero IV antibiotic durations and 1821 with available composite safety data.

There were 10 withdrawals of consent: 1 complete withdrawal; 3 from further treatment/trial intervention, active follow-up and questionnaires but allowed existing data and child's medical records to be used; 1 from further treatment/trial intervention but still participated in data collection; 4 from active follow-up only but allowed existing data and child's medical records to be used and 1 from future data linkage studies. A detailed CONSORT flow diagram in provided in *Figure 5*.

Baseline characteristics

Patient demographics and baseline characteristics are summarised by trial arm in *Table 9*. A more detailed breakdown of initial diagnoses is provided in *Table 10*, and of comorbidities in *Table 11*.

Primary analysis

Median IV antibiotic duration was 99.7 hours in the UC arm and 96.0 hours in the PCT arm, corresponding to an adjusted HR of 0.96 (95% CI 0.87, 1.05) with no evidence of a difference in IV antibiotic duration between arms (*Table 12*, *Figure 6*). There was no evidence of deviation from the PH assumption, based on the slope of the Schoenfeld residuals. Some patients had to be excluded from the final analysis because their duration of IV antibiotic use was zero (12 in the UC arm, 26 in the PCT arm) – either because they had not received IV antibiotics at all or because they were not put on IV antibiotics on the day of randomisation.

Patients' risk of experiencing at least one event covered by the composite safety outcome measure was 85/904 (9.4%) in the UC arm and 78/917 (8.5%) in the intervention arm, corresponding to an adjusted RD of −0.0081. The upper bound of the 95% CI of the RD for the safety composite outcome is at 0.0111 and thus entirely below the non-inferiority margin of 0.05, consistent with non-inferiority (see *Table 12*).

Sensitivity analyses

The observed risk in the UC arm (*Table 13*) was substantially lower than the 15% that was assumed when designing the trial. This would have resulted in loosening of the definition of non-inferiority. To investigate how this deviation from the assumed risk affected the conclusion of non-inferiority, we attempted two transformations as sensitivity analyses, leading to more stringent definitions. First, we used the arcsine transformation[41] to transform the non-inferiority margin for the RD. The transformed margin was 0.0396, so the estimated RD remained consistent with non-inferiority. Second, we estimated the treatment effect on the RR scale. The assumptions of the sample size calculation would have implied a non-inferiority margin of 1.33 on this scale. The CI for the RR was entirely below the 1.33, also consistent with non-inferiority.

Other sensitivity analyses are summarised in *Table 14*. Imputed composite safety outcomes were derived by assuming that all missing values in the PCT arm were safety events and all missing values in the UC arm were not ('worst case') or vice versa ('best case'). Odds ratios (ORs) from the best- and worst-case imputation models differ from those in the primary (complete-case) analysis, reflecting the large numbers of patients with missing outcome data. In the worst-case scenario, the CI (on the RD scale) includes the non-inferiority margin of 0.05, consistent with inferiority.

Secondary analysis

There was no evidence of a treatment effect on any secondary outcome (*Table 15*). For the time-to-event outcomes, there was no evidence of deviation from the PH assumption, based on the slope of the Schoenfeld residuals. Because there were no significant effects among the secondary analyses, we did not adjust for multiple testing as it was not necessary to control the false discovery rate.

Planned subgroup analyses

There was no evidence of differences in the treatment effect on the safety composite outcome between subgroups (*Table 16*). Subgroup analyses for the antibiotic duration outcome were not planned, because there was no significant treatment effect overall.

Post hoc subgroup analyses

Further subgroup analyses were added after results of the primary analysis were known. None of these provided any evidence of differences in the treatment effect between subgroups (*Table 17*).

TABLE 9 Descriptive statistics by arm

		PCT	UC
N		977	972
Age at randomisation in years [median (IQR)]		3.1 (0.8–8.8)	3.1 (0.7–8.7)
Age category, as used in minimisation (%)	0–6 months	202 (20.7)	211 (21.7)
	> 6 months–2 years	197 (20.2)	204 (21.0)
	> 2–5 years	196 (20.1)	176 (18.1)
	> 5 years	382 (39.1)	381 (39.2)
Sex (%)	Female	427 (43.7)	478 (49.2)
	Male	550 (56.3)	494 (50.8)
	Missing	0 (0)	0 (0)
Ethnicity (%)	Asian/Asian British	37 (3.8)	34 (3.5)
	Black/African/Caribbean/Black British	12 (1.2)	14 (1.4)
	Mixed/multiple ethnic groups	42 (4.3)	39 (4.0)
	Other ethnic group	10 (1.0)	8 (0.8)
	White	838 (85.8)	828 (85.2)
	Missing	38 (3.9)	49 (5.0)
Duration of symptoms at admission in hours [median (IQR)]		70 (24–144)	60 (24–120)
Prescribed antibiotic use in past 14 days (%)	No	549 (56.2)	552 (56.8)
	Yes	423 (43.3)	418 (43.0)
	Missing	5 (0.5)	2 (0.2)
Route of admission (%)	ED/AAU	532 (54.5)	534 (54.9)
	GP	19 (1.9)	20 (2.1)
	HDU	34 (3.5)	29 (3.0)
	Inpatient ward	62 (6.3)	60 (6.2)
	Other hospital	237 (24.3)	238 (24.5)
	PICU	42 (4.3)	35 (3.6)
	Theatre	48 (4.9)	55 (5.7)
	Missing	3 (0.3)	1 (0.1)
Comorbidities (%)	No	575 (58.9)	571 (58.7)
	Yes (1)	114 (11.7)	126 (13.0)
	Yes (2 +)	275 (28.1)	266 (27.4)
	Missing	13 (1.3)	9 (0.9)

continued

TABLE 9 Descriptive statistics by arm (*continued*)

		PCT	UC
Centre (%)	1	282 (28.9)	279 (28.7)
	2	270 (27.6)	269 (27.7)
	3	16 (1.6)	17 (1.7)
	4	143 (14.6)	145 (14.9)
	5	30 (3.1)	29 (3.0)
	6	113 (11.6)	110 (11.3)
	7	28 (2.9)	29 (3.0)
	8	15 (1.5)	14 (1.4)
	9	12 (1.2)	12 (1.2)
	10	6 (0.6)	6 (0.6)
	11	11 (1.1)	11 (1.1)
	12	20 (2.0)	19 (2.0)
	13	6 (0.6)	6 (0.6)
	14	21 (2.1)	20 (2.1)
	15	4 (0.4)	6 (0.6)
Number of PCT tests [median (IQR)]		2 (1–4)	

AAU, acute assessment unit.

TABLE 10 Initial diagnoses by arm

Initial diagnosis	PCT	UC
Bone/joint/muscle infection	86	99
Central nervous system infection	5	5
Fever alone	30	28
Flu-like illness	2	8
GIT/abdominal infection	147	128
Inflammatory syndrome	3	13
LRTI	213	221
None	5	4
Other	143	142
Otitis media	5	2
Pathogen syndrome	0	2
Sepsis syndrome	129	130
Soft-tissue infection	135	113
Tonsillitis/pharyngitis	16	15
Unknown	25	32
Urinary tract infection	89	94
Upper respiratory tract infection (other)	38	35

GIT, gastrointestinal; LRTI, lower respiratory tract infection.

Note
Each patient can have zero, one or multiple initial diagnoses.

TABLE 11 Comorbidities by arm

Comorbidity	PCT	UC
Allergic	57	48
Cardiac	122	117
Consanguinity	2	2
Endocrine	30	28
Foreign body	54	45
Gastrointestinal	117	112
Genetic	96	93
Immunodeficient	6	3
Important history	118	142
Malignancy	1	3
Neurological	120	137
Organ transplant	0	1
Prematurity	96	72
Pulmonary	74	63
Recent surgery	155	146

Note
Each patient can have zero, one or multiple comorbidities.

Adherence

Only 226 patients (23.1%) in the PCT arm were treated strictly in adherence with the protocol (*Table 18*). For 310 patients (31.7%), no PCT test result was ever considered. Possible consequences of low adherence include falsely claiming non-inferiority[57] with respect to the safety outcome and failure to detect superiority with respect to antibiotic use. For 366 patients (37.5%), no PCT test result was available at the first post-randomisation clinical review, suggesting that the process of obtaining PCT results was an obstacle to implementation.

Complier-average causal effect

Complier-average casual effect estimates were derived by two-stage regression, where the first stage was logistic regression of treatment received on treatment allocated (*Table 19*) and the second stage was either logistic regression or Cox regression of the outcome on the probability of receiving treatment (*Table 20*). Both stages were adjusted for age and for whether the patient was admitted at an AMS/non-AMS site, to approximate the adjustment made in the primary analysis with bootstrapped CIs.

For both outcomes, stricter definitions led to wider CIs (due to sample size) and larger effect estimates.

Summary of BATCH quantitative findings

There was no evidence of a treatment effect on any primary or secondary outcome, either overall or in any subgroup. The estimated treatment effect for the composite safety outcome was consistent with non-inferiority. We therefore conclude that making the results of the PCT-guided algorithm available to clinicians was non-inferior with respect to safety and ineffective with respect to antibiotic use.

TABLE 12 Treatment effect estimates for the primary outcomes

Outcome	Analysis	*N*	PCT	UC	Adjusted treatment effect (95% CI)
IV antibiotic duration[a]	Primary	1911	Median (IQR) = 96.0 hours (59.5–155.5 hours)	Median (IQR) = 99.7 hours (61.2–153.8 hours)	HR = 0.96 (0.87 to 1.05)
Safety composite[b]	Primary	1821	Frequency (%) 78/917 (8.5)	Frequency (%) = 85/904 (9.4)	OR = 0.89 (1.17) RD = −0.0081 (0.0111) RR = 0.90 (1.15)

OR, odds ratio
a Analysis method: Cox regression.
b Analysis method: logistic regression.

Note
Confidence intervals for the composite safety outcome are one-sided, with no lower bound. Covariates in all models: centre as a random effect and age as a fixed effect.

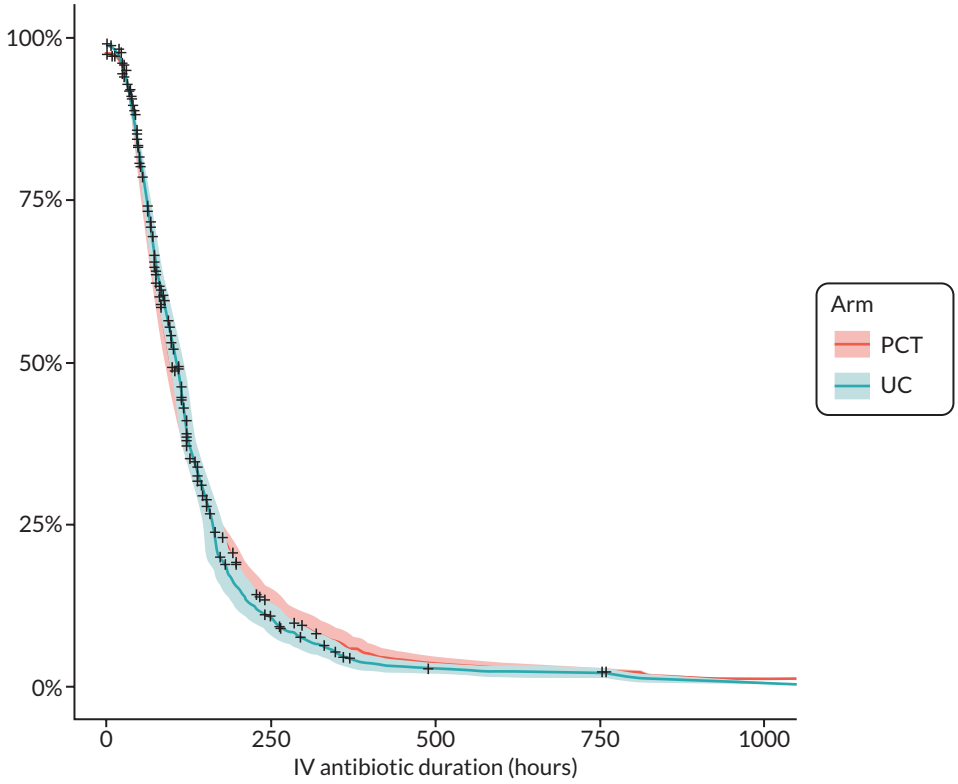

FIGURE 6 Kaplan–Meier estimates of the duration of IV antibiotics use in hours. +, censored observations due to unknown stopping times.

TABLE 13 Proportion of patients experiencing the composite safety outcome, its components, or secondary safety outcomes

Outcome	Level	PCT	UC
Composite safety outcome (%)	No	839 (85.9)	819 (84.3)
	Yes	78 (8.0)	85 (8.7)
	Missing	60 (6.1)	68 (7.0)
Unscheduled re-admission (%)	No	876 (89.7)	859 (88.4)
	Yes	39 (4.0)	42 (4.3)
	Missing	62 (6.3)	71 (7.3)
Restarted IV antibiotics (%)	No	869 (88.9)	861 (88.6)
	Yes	51 (5.2)	50 (5.1)
	Missing	57 (5.8)	61 (6.3)
Mortality (%)	No	941 (96.3)	925 (95.2)
	Yes	6 (0.6)	11 (1.1)
	Missing	30 (3.1)	36 (3.7)
HAI (%)	No	868 (88.8)	872 (89.7)
	Yes	26 (2.7)	19 (2.0)
	Missing	83 (8.5)	81 (8.3)
Suspected ADR (%)	No	859 (87.9)	869 (89.4)
	Yes	15 (1.5)	10 (1.0)
	Missing	103 (10.5)	93 (9.6)

TABLE 14 Treatment effect estimates for sensitivity analyses of the primary outcomes

Outcome	Analysis	*n*	PCT	UC	Adjusted treatment effect (95% CI)
IV antibiotic duration[a]	Excluding ineligible patients	1908	Median (IQR) = 96.0 hours (59.5–155.6 hours)	Median (IQR) = 99.6 hours (61.1–153.7 hours)	HR = 0.96 (0.87 to 1.05)
Safety composite[b]	Excluding ineligible patients	1806	Frequency (%) = 78/908 (8.6)	Frequency (%) = 85/898 (9.5)	OR = 0.90 (1.17) RD = −0.0079 (0.0116) RR = 0.90 (1.16)
	Best-case imputation	1949	Frequency (%) = 78/977 (8.0)	Frequency (%) = 153/972 (15.7)	OR = 0.46 (0.58) RD = −0.06 (−0.03) RR = 0.50 (0.62)
	Worst-case imputation	1949	Frequency (%) = 138/977 (14.1)	Frequency (%) = 85/972 (8.7)	OR = 1.74 (2.22) RD = 0.04 (0.0) RR = 1.64 (2.04)

OR, odds ratio
a Analysis method: Cox regression.
b Analysis method: logistic regression.

Note
Confidence intervals for the composite safety outcome are one-sided, with no lower bound. Covariates in all models: centre as a random effect and age as a fixed effect.

TABLE 15 Treatment effect estimates for the secondary outcomes

Outcome	*n*	PCT	UC	Adjusted treatment effect (95% CI)
Total (IV, oral, IM) duration of antibiotic use[a]	1911	Median (IQR) = 113.4 hours (67.4–179.7 hours)	Median (IQR) = 113.5 (68.9–166.7 hours)	HR = 0.95 (0.86 to 1.04)
Duration of broad-spectrum antibiotic use[a]	1797	Median (IQR) = 104.0 hours (62.2–167.5 hour)	Median (IQR) = 108.4 (65.9–159.4 hours)	HR = 0.95 (0.86 to 1.04)
Time to discharge from hospital[a]	1888	Median (IQR) = 96.0 hours (48.0–240.0 hours)	Median (IQR) = 120.0 hours (48.0–263.5 hours)	HR = 1.01 (0.92 to 1.10)
Unscheduled re-admission[b]	1816	Frequency (%) = 39/915 (4.3)	Frequency (%) = 42/901 (4.7)	OR = 0.91 (0.58 to 1.42)
Restarted IV antibiotics[b]	1831	Frequency (%) = 51/920 (5.5)	Frequency (%) = 50/911 (5.5)	OR = 1.01 (0.67 to 1.51)
Mortality[b]	1883	Frequency (%) = 6/947 (0.6)	Frequency (%) = 11/936 (1.2)	OR = 0.54 (0.20 to 1.46)
HAI[b]	1785	Frequency (%) = 26/894 (2.9)	Frequency (%) = 19/891 (2.1)	OR = 1.38 (0.75 to 2.53)
Suspected ADR[b]	1753	Frequency (%) = 15/874 (1.7)	Frequency (%) = 10/879 (1.1)	OR = 1.50 (0.66 to 3.38)

OR, odds ratio
a Analysis method: Cox regression.
b Analysis method: logistic regression.

Note
Covariates in all models: centre as a random effect and age as a fixed effect.

TABLE 16 Planned subgroup analyses

Outcome	Subgroups	*N*	LRT X^2 (df)	*p*-value
Safety composite	Organ system of infection[a]	1530	4.42 (5)	0.49
	Soft tissue/bone/joint/muscle	405	PCT: frequency (%) = 10/209 (4.8) UC: frequency (%) = 12/196 (6.1)	
	Gastrointestinal/abdominal	253	PCT: frequency (%) = 12/134 (9.0) UC: frequency (%) = 20/119 (16.8)	
	Urinary tract	180	PCT: frequency (%) = 7/88 (8.0) UC: frequency (%) = 4/92 (4.3)	
	Sepsis syndrome	244	PCT: frequency (%) = 10/121 (8.3) UC: frequency (%) = 10/123 (8.1)	
	Lower respiratory	396	PCT: frequency (%) = 24/195 (12.3) UC: frequency (%) = 23/201 (11.4)	
	Recruited before/after COVID-19 pause	1821	0.04 (1)	0.84
	Before	1012	PCT: frequency (%) = 44/503 (8.7) UC: frequency (%) = 48/509 (9.4)	
	After	809	PCT: frequency (%) = 34/414 (8.2) UC: frequency (%) = 37/395 (9.4)	

df, degrees of freedom.

a Patients can have infection in more than one organ system.

Note

Interaction tests by model comparison. Covariates in all models: centre as a random effect and age as a fixed effect.

TABLE 17 Post hoc subgroup analyses

Outcome	Subgroups	*N*	LRT X^2 (df)	*p*-value
IV antibiotic duration[a]	Organ system of infection[c]	1510	9.37 (5)	0.10
	Soft tissue/bone/joint/muscle	419	PCT: median (IQR) = 90.8 hours (59.6–167.0 hours) UC: median (IQR) = 84.8 hours (58.4–160.0 hours)	
	Gastrointestinal/abdominal	274	PCT: median (IQR) = 121.9 hours (73.8–191.0 hours) UC: median (IQR) = 116.6 hours (80.0–165.0 hours)	
	Urinary tract	177	PCT: median (IQR) = 68.2 hours (44.8–90.5 hours) UC: median (IQR) = 83.9 hours (50.5–120.7 hours)	
	Sepsis syndrome	256	PCT: median (IQR) = 97.5 hours (56.1–146.3 hours) UC: median (IQR) = 98.4 hours (51.4–159.0 hours)	
	Lower respiratory	430	PCT: median (IQR) = 106.2 hours (64.5–170.2 hours) UC: median (IQR) = 118.5 hours (70.5–162.8 hours)	
	Recruited before/after COVID-19 pause	1911	0.13 (1)	0.71
	Before	1057	PCT: median (IQR) = 98.0 hours (63.9–154.0 hours) UC: median (IQR) = 104.0 hours (63.4–160.0 hours)	
	After	854	PCT: median (IQR) = 90.7 hours (54.0–157.5 hours) UC: median (IQR) = 96.8 hours (59.5–146.1 hours)	
	AMS/non-AMS sites	1911	0.98 (1)	0.32
	AMS	1581	PCT: median (IQR) = 99.0 hours (59.9–161.0 hours) UC: median (IQR) = 107.8 hours (63.1–161.1 hours)	
	Non-AMS	330	PCT: median (IQR) = 84.0 hours (56.0–120.9 hours) UC: median (IQR) = 79.9 hours (54.0–121.2 hours)	
	Recent surgery	1911	2.06 (1)	
	Yes	300	PCT: median (IQR) = 114.4 hours (72.0–187.6 hours) UC: median (IQR) = 130.3 hours (75.9–201.7 hours)	
	No	1611	PCT: median (IQR) = 92.0 hours (56.9–148.1 hours) UC: median (IQR) = 95.7 hours (59.1–144.6 hours)	

TABLE 17 Post hoc subgroup analyses (*continued*)

Outcome	Subgroups	*N*	LRT X^2 (df)	*p*-value
Safety composite[b]	AMS/non-AMS sites	1821	0.00 (1)	0.99
	AMS	1484	PCT: frequency (%) = 71/749 (9.5) UC: frequency (%) = 77/735 (10.5)	
	Non-AMS	337	PCT: frequency (%) = 7/168 (4.2) UC: frequency (%) = 8/169 (4.7)	
	Recent surgery	1821	0.40 (1)	0.53
	Yes	282	PCT: frequency (%) = 17/143 (11.9) UC: frequency (%) = 21/139 (15.1)	
	No	1539	PCT: frequency (%) = 61/774 (7.9) UC: frequency (%) = 64/765 (8.4)	

df, degrees of freedom.
a Analysis method: Cox regression.
b Analysis method: logistic regression.
c Patients can have infection in more than one organ system.
Interaction tests by model comparison. Covariates in all models: centre as a random effect and age as a fixed effect.

TABLE 18 Summary of adherence in the PCT arm, summarised per patient as counts with percentages, and descriptive summaries of coprimary outcomes by level of adherence

Step	Frequency	Level	PCT	IV antibiotic duration: median (IQR)	Safety composite: frequency (%)
1. PCT available…	…at all clinical reviews	No	588 (60.2)	103.0 hours (62.7–170.6 hours)	54/553 (9.8)
		Yes	360 (36.8)	84.7 hours (55.1–136.2 hours)	22/338 (6.5)
		Missing	29 (3.0)		
	…at any clinical review	No	173 (17.7)	71.2 hours (44.5–115.0 hours)	5/163 (3.1)
		Yes	775 (79.3)	104.0 hours (63.7–167.5 hours)	70/728 (9.6)
		Missing	29 (3.0)		
	…at first clinical review	No	366 (37.5)	88.0 hours (54.0–142.1 hours)	25/346 (7.2)
		Yes	583 (59.7)	102.2 hours (62.4–167.4 hours)	50/546 (9.2)
		Missing	28 (2.9)		
2. PCT considered…	…at all clinical reviews	No	713 (73.0)	100.0 hours (60.8–167.4 hours)	65/673 (9.7)
		Yes	226 (23.1)	80.1 hours (55.4–135.0 hours)	11/211 (5.2)
		Missing	38 (3.9)		
	…at any clinical review	No	310 (31.7)	84.0 hours (49.0–136.7 hours)	15/291 (5.1)
		Yes	618 (63.3)	103.0 hours (64.3–164.0 hours)	58/582 (10.0)
		Missing	49 (5.0)		
	…at first clinical review	No	501 (51.3)	94.1 hours (57.3–154.3 hours)	37/473 (7.8)
		Yes	438 (44.8)	97.0 hours (62.3–157.5 hours)	38/410 (9.3)
		Missing	38 (3.9)		

TABLE 18 Summary of adherence in the PCT arm, summarised per patient as counts with percentages, and descriptive summaries of coprimary outcomes by level of adherence (*continued*)

Step	Frequency	Level	PCT	IV antibiotic duration: median (IQR)	Safety composite: frequency (%)
3. Algorithm adhered to…	…at all clinical reviews	No	787 (80.6)	96.4 hours (60.2–159.9 hours)	70/741 (9.4)
		Yes	153 (15.7)	87.0 hours (58.2–139.5 hours)	6/144 (4.2)
		Missing	37 (3.8)		
	…at any clinical review	No	395 (40.4)	84.1 hours (50.2–136.7 hours)	19/372 (5.1)
		Yes	527 (53.9)	104.7 hours (64.5–167.6 hours)	53/495 (10.7)
		Missing	55 (5.6)		
	…at first clinical review	No	587 (60.1)	92.2 hours (56.0–151.3 hours)	46/554 (8.3)
		Yes	352 (36.0)	102.0 hours (63.7–167.0 hours)	29/329 (8.8)
		Missing	38 (3.9)		

Note
Perfect adherence is assumed in the UC arm. Strict adherence to the protocol requires that PCT results are available and are considered (step 2) at each clinical review but does not require the clinical decision to agree with the recommendations of the PCT algorithm (step 3).

TABLE 19 Complier-average causal effect estimates for the composite safety outcome

Step	Frequency	*N*	CACE (95% CI)
1. PCT available…	…at all clinical reviews	1795	RD = −0.023 (0.039)
	…at any clinical review	1795	RD = −0.013 (0.014)
	…at first clinical review	1796	RD = −0.016 (0.020)
2. PCT considered…	…at all clinical reviews	1788	RD = −0.031 (0.070)
	…at any clinical review	1777	RD = −0.015 (0.018)
	…at first clinical review	1787	RD = −0.018 (0.029)
3. Algorithm adhered to…	…at all clinical reviews	1789	RD = −0.040 (0.109)
	…at any clinical review	1771	RD = −0.018 (0.020)
	…at first clinical review	1787	RD = −0.021 (0.040)
By allocated treatment arm (compare primary analysis)		1821	RD = −0.0092 (0.0124)

Note
Analysis method: logistic regression (stages 1 and 2). Confidence intervals for the composite safety outcome are one-sided, with no lower bound. Covariates in all models: AMS/non-AMS site and age as fixed effects.

TABLE 20 Complier-average causal effect estimates for IV antibiotic duration

Step	Frequency	*N*	CACE (95% CI)
1. PCT available…	…at all clinical reviews	1920	HR = 0.88 (0.69 to 1.14)
	…at any clinical review	1920	HR = 0.95 (0.85 to 1.07)
	…at first clinical review	1921	HR = 0.94 (0.81 to 1.10)
2. PCT considered…	…at all clinical reviews	1911	HR = 0.82 (0.56 to 1.22)
	…at any clinical review	1900	HR = 0.93 (0.81 to 1.07)
	…at first clinical review	1911	HR = 0.92 (0.76 to 1.14)
3. Algorithm adhered to…	…at all clinical reviews	1912	HR = 0.79 (0.45 to 1.40)
	…at any clinical review	1894	HR = 0.92 (0.79 to 1.09)
	…at first clinical review	1911	HR = 0.91 (0.71 to 1.17)
By allocated treatment arm (compare primary analysis)		1949	HR = 0.97 (0.89 to 1.07)

Note
Analysis method: logistic regression (stage 1), Cox regression (stage 2). Covariates in all models: AMS/non-AMS site and age as fixed effects.

Chapter 4 Health economics results

Introduction

This chapter presents the health economic analysis of BATCH, a within-trial incremental cost-effectiveness analysis comparing the PCT-guided management in children with SBI and the standard clinical management.

Following NICE guidelines, our analysis adopted an NHS and personal social services perspective. We took into account the costs associated with the BATCH intervention, as well as costs related to health care provided in a hospital setting, primary care, emergency services and medicines. When calculating the costs of the intervention, we employed a micro-costing approach. Costs are presented in Great British pounds (GBP) and updated to 2021 cost figures using the NHS cost inflation index when required. To assess the impact on health outcomes, we measured the patients' utilities using the CHU9D, a HRQoL measure for children. Further to NICE's perspective, we have also accounted for family productivity losses.

Aims and objectives

The aim of health economic analysis was to determine the cost-effectiveness of PCT-guided antibiotic treatment compared with UC for children with suspected or confirmed bacterial infection. The main outcome measures include duration of IV antibiotic treatment, safety of PCT-guided treatments and healthcare costs. Specific objectives were to determine:

- average cost of a hospital episode
- changes in health utility (CHU9D) from baseline and up to day 28.

Method: costs

Chapter 2 provides information on the trial design, setting, selection of sites and participant, recruitment, screening, randomisation, follow-up assessments and effectiveness outcomes. Following NICE guidance, the costs were identified from an NHS and patient's perspective. Costs of real-world delivery within the trial were used. This study employed a micro-costing approach[58] to value the resources used. All relevant resources expended at patient level were identified and recorded by research nurses. This includes but is not limited to inpatient events, diagnostic tests, medications, and GP and emergency visits. The unit costs of each resource were obtained following NICE guidelines. This allows us to examine the cost difference by the resource category between the PCT and UC arms.

To conduct the cost-effectiveness analysis, we identified the cost differences between the treatment and control arms and estimated the ICER. The ICERs were calculated as the cost per IV antibiotic hours avoided with increased or equal safety.

The secondary outcome measure was the health utility of the patients measured by CHU9D, a measure of HRQoL specifically designed for paediatric patients.[30] We conducted a utility analysis that estimates the marginal change in health utility from the baseline to the 28th day since randomisation.

Costs of healthcare and social services

Data on diagnostic laboratory tests, the length of stay and details regarding antibiotic prescriptions were collected during hospital admissions by research nurses. Specifically, the data contain information on the type of clinical tests performed, the number of inpatient bed-days (rounded to the nearest half day), the type of antibiotics prescribed, the administration route, the dosage administered and the duration of antibiotic treatment. Following NICE guidelines, we obtained information on the cost of antibiotic prescriptions from NHS Electronic Drug Tariff 2023 which contains

data regarding the prices paid for certain drugs by NHS trusts. If the cost is not listed in the NHS Electronic Drug Tariff, the drug tariff indicated in the BNF were used. *Appendix 2* presents the cost of antibiotic prescriptions covered in the analysis.

A questionnaire was designed for this study with an aim of collecting information on the additional use of a comprehensive range of healthcare services within 28 days following randomisation. The parents of the children were asked to complete the follow-up questionnaire on behalf of their children. The information collected included GP and nurse consultations/treatments (number of GP/nurse visits), hospital emergency visits, hospital clinic visits, OPAT, overnight hospital stays and additional travelling expenses.

Children aged over 7 years were also invited to fill out the same questionnaire. However, only 18 children and young people (representing 1% of the total sample) completed the questionnaire. Consequently, the data obtained from children aged over 7 were not used in this study.

Another set of questions covered the use of additional medication prescribed to be taken at home and the use of over-the-counter medicines within the 28-day follow-up period. Patients' parents reported antibiotic prescriptions prescribed since randomisation (including type, dose and duration), and over-the-counter medication (including type, dose and duration). *Appendix 3* lists the follow-up medication name, price and unit price. For PICU and paediatric high dependency unit (PHDU) admissions, data included the date and time of re-admission, but there was no discharge date for each period of re-admission. Therefore, the average length of stay was used to compute the costs: 1.8 days for PICU and 2 days for PHDU admissions.

The unit costs were obtained from several sources including Unit Costs of Health and Social Care 2021, National Schedule of NHS Costs – Year 2020–1 and Routine Preoperative Tests for Elective Surgery 2015. Unit cost used included overheads, capital and infrastructure costs, allocated according to staff time. Information on average travel distance for home visits was not available. The average time per surgery consultation was 9.22 minutes excluding travel. In our analysis, a unit cost of £14 per PCT test was used.[59] The costs obtained from Routine Preoperative Tests for Elective Surgery 2015 were updated to 2021 using the NHS inflation index.

Table 21 lists the unit costs of a wide range of healthcare and social resources used in the analysis. Unit costs of non-admitted attendance, day case, regular day or night admissions, and paediatric hospital inpatient covered only attendances associated with paediatric IDs. Unit costs of accident and emergency (A&E) visits included both admitted and non-admitted patients.

Health outcomes

To measure the HRQoL of the patients, the CHU9D index was used to assess health outcomes. CHU9D considers nine dimensions of paediatric patients' well-being including worry, sadness, pain, tiredness, annoyance, schoolwork, sleep, daily routine and ability to join activities. Each dimension consists of five levels: no problems, slight problems, some problems, many problems and extreme problems. An existing study[30] provides a set of preference weights for health states defined by CHU9D obtained from interviews with 300 UK adults. We utilised the preference weights and calculated the CHU9D index score for parents of the children who completed the questionnaire. The index score ranges between 0 and 1, where 0 represents the worst possible health state and 1 represents the best health state.

The CHU9D questionnaire was administered at two time points: baseline and 28 days post randomisation. Parents of the patients were requested to fill out the CHU9D questionnaire on behalf of their children. For children aged 7 years and older, they were also individually asked to complete the CHU9D questionnaire themselves.

The CHU9D index score can be converted to quality-adjusted life-years (QALYs). However, QALYs were not presented in this study because only one set of follow-up CHU9D scores were available at 28 days after randomisation.

Parents' productivity losses

Patients' parents were asked about their productivity losses during their children's stay in hospital and since discharge, respectively, at the point of 28-day follow-up, which included questions about the number of days absent from work, income losses, and additional expenses incurred for child-care costs.

TABLE 21 National average unit cost used in BATCH health economic analysis

Resource	Costs (£)	Unit	Source
PCT test	14.00	Test	Protocol for serum procalcitonin testing in medical admissions
Blood	6.49	Test	Routine preoperative tests for elective surgery 2015[a]
CSF analysis	6.49	Test	Routine preoperative tests for elective surgery 2015[a]
MRI	307.22	Scan	Routine preoperative tests for elective surgery 2015[a]
CT	157.97	Scan	Routine preoperative tests for elective surgery 2015[a]
Ultrasound	57.63	Scan	Routine preoperative tests for elective surgery 2015[a]
Paediatric hospital inpatient	2603.39	Day	National Schedule of NHS Costs – Year 2020–1
Paediatric intensive care (face to face)	2907.60	Day	National Schedule of NHS Costs – Year 2020–1
Paediatric consultant-led outpatient	224.00	Attendance	Unit Costs of Health and Social Care 2021
PHDU	1339.00	Day	National Schedule of NHS Costs – Year 2020–1
A&E	296.88	Attendance	National Schedule of NHS Costs – Year 2020–1
Specialist nursing, infectious diseases, child, face to face	89.00	Contact	National Schedule of NHS Costs – Year 2020–1
NHS 111/NHS Direct	89.59	Calls	National Schedule of NHS Costs – Year 2020–1
GP (face to face, normal surgery hours)	39.00	Contact	Unit Costs of Health and Social Care 2021
GP (home visit)	148.31	Contact	Unit Costs of Health and Social Care 2010
Nurse (GP practice)	44.00	Hour	Unit Costs of Health and Social Care 2021

a Costs have been uprated to 2021 figures using the NHS cost inflation index (see *Appendix 4*, also available at www.pssru.ac.uk/pub/uc/uc2021/sourcesofinformation.pdf) (accessed 26 June 2023).

Methods: analysis

Cost-effectiveness analysis

In our analysis, we calculated the ICER, focusing on a clinically effective outcome that entails a reduction in the number of days on IV antibiotics while ensuring equal or enhanced safety outcomes. In accordance with the identification of costs, we conducted an estimation of the average cost per patient for each intervention arm over the trial. We first calculated the difference in the average cost per patient between the two arms of the trial. Then, we compared the number of IV antibiotics days between the two arms. The ICER was the ratio of the cost difference to the difference in the median number of IV antibiotics days.

Equation 1: Incremental cost-effectiveness ratio

$$ICER = \frac{\Delta((\text{cost}_{\text{int ervention arm}} + \text{int ervention cos t}) - \text{cos t}_{\text{comparator arm}})}{\Delta \text{ number of hours on IV antibiotics}}$$

To account for uncertainty in cost-effectiveness outcomes, bootstrapping was used to derive CIs. More specifically, we randomly selected 1949 patients, with replacement, from the original sample to create 1000 bootstrap samples. Each bootstrap sample is of the same size as the original data set, 1949. By repeatedly resampling from the observed data, non-parametric bootstrapping captured the variability present in the original sample and allowed us to assess the uncertainty associated with statistical estimates. Then, we estimated the outcome variables using the bootstrap samples. The predicted outcome variables were used to estimate the 95% CIs for incremental costs and incremental outcomes. Those results were also used to plot the cost-effectiveness plane to show the uncertainty surrounding conclusions.

Missing data

To address issue of missing values, we employed a multiple imputation with chained equations (MICE) system.[60] The MICE was performed using a STATA package 'ice'[61] which imputes missing values by using a linear multivariable regression. In the regression, the 28-day outcome variables were predicted by patient characteristics including age, gender, ethnicity and the baseline outcomes variables.

The percentage of missing values can be as high as 67% for some CHU9D dimensions. MICE may be one of the best ways to mitigate the concern of a large number of missingness. To fill the missing values, we used the following methods:

Step 1: We used logistic regressions to identify the association between missing values and patients' characteristics,

$$\text{Logit}(\text{Missing}_{ij}) = \alpha_0 + \alpha_1 \text{Age}_i + \alpha_2 \text{Gender}_i + \alpha_2 \text{Allocation}_i + \delta \text{ETHNICITY}_i + \varepsilon_i$$

where

Missing_{ij} is set to 1 if the variable *j* for patient *i* is not missing, and 0 otherwise,

Gender_i is equal to 1 if patient *i* is a boy, and 0 if patient *i* is a girl,

Allocation_i is equal to 1 if patient *i* was allocated to the PCT arm, and 0 otherwise,

ETHNICITY is a vector containing a list of 18 ethnicity groups,

ϵ_i is the error term.

Results from the logistic regressions show that only patient's age is statistically significantly associated with the missingness. The ORs are in the range between 0.80 and 0.95, suggesting that parents of older children tended to report fewer missing values. This indicates that it may be more difficult for parents of infants (and younger children) to understand their children's feelings. All other predictors are not statistically significant.

Step 2: A parametric method, MICE, was used to fill the missingness. There are nine CHU9D dimensions (worried, sad, annoyed, tired, pain, sleep, daily routine, school and ability to join activities) recorded at both baseline and 28-day follow-up. We assumed that the level of each dimension at 28-day follow-up is associated with the same dimension at the baseline and the patient's demographic characteristics (including allocation, age, gender and ethnicity). Similarly, the level of each dimension at the baseline is associated with the same dimension at the 28-day follow-up and the patient's demographic characteristics.

The number of imputations was set at 20 (m = 20), because the fraction of missing information (FMI) for some dimensions can be over 75%. If we can accept 5% loss of efficiency (i.e. FMI/m ≤ 0.05), the number of imputations has to be > 15.

Step 3: Then, we combined and analysed the 20 imputed data sets using Rubin's rules.

Sensitivity analyses

Bootstrap sampling can introduce uncertainty associated with the observed data by resampling from the data set itself. We tested the robustness of the ICER by also undertaking a complete-case analysis as a secondary analysis, as this uses alternative assumptions from those informing the multiple imputation.

Valuing parents' productivity losses

The financial losses due to off work were valued using the national average daily earnings 2021 (£122.20 per day) published by the Office of National Statistics.[62] The parents were also asked to disclose any immediate financial losses and additional child-care costs occurred measured in GBP sterling. We compared the differences in each productivity loss item between the two arms using a paired sample *t*-test.

Results

Costs

Table 22 reports the summary of primary outcomes from the original data sets, IV antibiotic duration and the safety indicator. Overall, the median IV antibiotic durations across all age groups in the PCT arm are lower than those in the UC arm (non-significant).

Regarding the composite safety outcome, our results indicate that 8.51% of the patients in the PCT arm and 9.40% of patients in the UC arm experienced unscheduled hospitalisation or death. Using Wilcoxon rank-sum tests, we found no statistically significant differences in the distribution of the composite safety outcome between the two arms (under 5, $p = 0.84$, over 5, $p = 0.44$, all ages, $p = 0.50$).

Table 23 summarises the percentage of patients who experienced unscheduled admissions, restarted IV antibiotics, mortality, HAIs and suspected ADRs. The missingness was excluded when calculating the percentages. Compared with UC, there are fewer patients experiencing re-admissions in the PCT arm. However, there are more patients experiencing HAIs and suspected ADRs in the PCT arm.

Table 24 reports the average number and cost of diagnostic tests including PCT test, blood test, cerebrospinal fluid (CSF) analysis, magnetic resonance imaging (MRI), computed tomography (CT) and ultrasound. Our results show that the diagnostic costs in the PCT arm are similar to the costs in the UC arm.

Table 25 indicates that the costs of antibiotics are slightly lower in the PCT arm during patient's stay in hospital and the biggest difference is found in children aged 5 and over.

Tables 26 and *27* summarise the number and costs of inpatient bed-days and OPAT attendance. Overall, the length of stay is lower in the PCT group for children under 5 (−2.83 days on average per admission). However, for children aged 5 and above, length of stay is higher in the PCT group by around 6 days. On average, for all age groups, children in the PCT group stay in the hospital for an extra 0.8 days and cost an additional £2000 (see *Table 27*).

Table 28 summarises the costs of additional medications up to 28 days post randomisation. We found that the PCT arm reports a lower follow-up medication cost per patient in all age groups.

Table 29 shows that the overall utilisation of healthcare consultations over the 28-day follow-up period is similar between the two arms. At least one type of healthcare consultant was utilised by 66.9% of the patients in the PCT arm and by 69.5% of the patients in the UC arm. However, the PCT arm reported a lower rate of A&E visits and a lower rate of hospital visits. *Table 30* shows associated costs.

Primary outcome

Results for outcomes and incremental costs and effectiveness based on imputed data sets are presented in the *Tables 31–33* as means with standard error (SE). *Table 31* shows that costs related to hospital stays were the largest component, as usual in this type of analysis, followed by the cost of antibiotics and other medicines over the trial. Estimated average costs are higher for patients in the intervention group for children aged 5 and over and for all age groups, and higher for the patients in the control group for children under 5.

The PCT test contributed to a reduced duration of IV antibiotic even if not significantly different between groups.

To remove the impact of outliers from the bootstrapping results, average costs were also estimated without outliers (see *Table 32*).

Table 33 presents the bootstrap estimates of the median IV antibiotic duration. Results are similar to the results from the original sample reported in *Table 22*. The PCT-guided treatment leads to a lower IV antibiotic duration across all age groups compared to the UC arm.

TABLE 22 Median IV antibiotic duration and safety outcome by age group and trial arm

	PCT			UC		
	Median	SD	*N*	Median	SD	*N*
	(1)	(2)	(3)	(4)	(5)	(6)
IV antibiotic duration (hours)						
Under 5	91.68	399.73	578	94.73	121.72	591
Aged 5 and over	106.28	211.48	373	112.35	157.27	381
All age groups	96.00	338.58	951	99.67	137.24	960
	%	SD	*N*	%	SD	*N*
	(1)	(2)	(3)	(4)	(5)	(6)
Composite safety outcome (dummy variable)						
Under 5	8.00	0.27	550	8.33	0.28	540
Aged 5 and over	9.26	0.29	367	10.99	0.31	364
All age groups	8.51	0.28	917	9.40	0.29	904

TABLE 23 Summary of safety review by age group and trial arm

	PCT		UC	
	%	*N*	*%*	*N*
	(1)	(2)	(3)	(4)
Unscheduled admissions/re-admissions				
Under 5	3.83	549	3.53	538
Aged 5 and over	4.92	366	6.34	363
All age groups	4.26	915	4.65	901
Restarted IV antibiotics				
Under 5	5.25	552	4.75	547
Aged 5 and over	5.98	368	6.59	364
All age groups	5.54	920	5.45	911
Mortality				
Under 5	0.70	574	1.41	567
Aged 5 and over	0.54	373	0.81	369
All age groups	0.63	947	1.18	936
HAIs				
Under 5	3.33	541	2.25	534
Aged 5 and over	2.27	353	1.96	357
All age groups	2.91	894	2.13	891
Suspected ADRs				
Under 5	0.96	523	0.57	525
Aged 5 and over	2.85	351	1.98	354
All age groups	1.72	874	1.14	879

TABLE 24 Number and cost of diagnostic tests, including PCT, by age group and trial arm

	PCT			UC		
	Average number	Average cost (£)	*N*	Average number	Average cost (£)	*N*
	(1)	(2)	(3)	(4)	(5)	(6)
Under 5	10.48	197.55	590	10.90	193.18	587
Aged 5 and over	11.30	247.26	380	10.53	218.28	379
All age groups	10.80	217.03	970	10.75	203.02	966

TABLE 25 Costs (£) of antibiotics during hospital stay by age group and trial arm

	PCT			UC		
	Mean	SD	*N*	Mean	SD	*N*
	(1)	(2)	(3)	(4)	(5)	(6)
Under 5	38.47	71.22	592	39.26	70.80	589
Aged 5 and over	132.02	216.76	377	138.26	227.03	379
All age groups	74.86	153.06	969	78.02	159.80	968

TABLE 26 Number of inpatient bed-days and OPAT attendance by age group and trial arm

	PCT			UC		
	Mean	SD	*N*	Mean	SD	*N*
	(1)	(2)	(3)	(4)	(5)	(6)
PICU (days)						
Under 5	3.20	10.87	545	3.79	12.91	550
Aged 5 and over	2.19	10.06	363	1.71	5.05	361
All age groups	2.80	10.56	908	2.97	10.57	911
PHDU (days)						
Under 5	2.10	20.44	545	2.15	11.90	550
Aged 5 and over	1.30	5.62	363	1.10	4.91	361
All age groups	1.78	16.22	908	1.73	9.76	911
Ward/paediatric hospital inpatient (days)						
Under 5	9.97	33.00	545	10.32	38.12	550
Aged 5 and over	14.08	56.94	363	8.67	13.51	361
All age groups	11.61	44.17	908	9.67	30.81	911
OPAT (attendance)						
Under 5	0.70	4.30	545	0.70	3.19	550
Aged 5 and over	0.82	3.18	363	0.57	2.30	361
All age groups	0.75	3.89	908	0.65	2.87	911

TABLE 27 Costs (£) of inpatient bed-days (including PICU, PHDU and ward) and OPAT by age group and trial arm

	PCT			UC		
	Mean	SD	*N*	Mean	SD	N
	(1)	(2)	(3)	(4)	(5)	(6)
Inpatient bed-days (£)						
Under 5	38.05	100.92	545	40.78	113.09	550
Aged 5 and over	44.77	153.27	363	29.02	42.23	361
All age groups	40.74	124.48	908	36.12	91.95	911
OPAT (£)						
Under 5	157.42	962.97	545	156.39	714.38	550
Aged 5 and over	182.66	713.09	363	127.82	516.29	361
All age groups	167.51	871.37	908	145.07	643.06	911

TABLE 28 Costs (£) of additional medications up to 28 days post randomisation by age group and trial arm

	PCT			UC		
	Mean	SD	*N*	Mean	SD	*N*
	(1)	(2)	(3)	(4)	(5)	(6)
Under 5	41.57	118.25	592	61.56	195.16	591
Aged 5 and over	88.67	240.08	380	100.42	268.22	379
All age groups	59.99	117.59	972	76.74	227.19	970

TABLE 29 Quantity, percentage and number of users of healthcare services up to 28 days post randomisation, all age groups, by trial arm

	PCT			UC		
	Average quantity	% of patients	*N*	Average quantity	% of patients	*N*
	(1)	(2)	(3)	(3)	(4)	(5)
GP (normal surgery hours)	0.211	15.8	730	0.199	17.0	725
GP home visit	0.010	0.7	730	0.004	0.3	725
GP nurse consultation	0.137	4.5	730	0.121	5.4	725
Telephone with GP	0.123	7.9	730	0.194	11.9	725
A&E visits	0.208	16.4	730	0.259	19.0	725
Hospital clinic	0.164	9.7	730	0.174	9.2	725
NHS 111	0.026	2.1	730	0.025	2.2	725
OPAT visit (attendance)	0.490	8.2	730	0.428	8.4	725
Stay in hospital (nights)	0.575	10.4	730	0.632	13.5	725
Had at least one type of healthcare contact	–	66.9	730	–	69.5	725

TABLE 30 Costs (£) of healthcare services use up to 28 days post randomisation, all age groups, by users by trial arm

	PCT			UC		
	Mean	SD	*N*	Mean	SD	*N*
	(1)	(2)	(3)	(4)	(5)	(6)
GP (normal surgery hours)	8.23	21.20	730	7.75	18.75	725
GP home visit	1.42	19.75	730	0.61	12.31	725
GP nurse consultation	6.03	59.75	730	5.34	32.18	725
Telephone with GP	6.25	26.36	730	9.86	37.01	725
A&E visits	61.82	157.18	730	76.98	201.42	725
Hospital clinic	770.32	2853.32	730	814.41	3286.47	725
NHS 111	2.33	17.72	730	2.22	15.46	725
OPAT visit (attendance)	109.85	520.12	730	95.78	476.30	725
Stay in hospital (nights)	1497.84	6258.04	730	1644.62	5903.33	725
Total	2464.09	7060.00	730	2657.59	6994.00	725

TABLE 31 Estimated average cost (£) per patient from the bootstrap samples by age group and trial arm

	PCT				UC			
	Coefficient	SE	95% CI		Coefficient	SE	95% CI	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Under 5	26,532	2817	21,010	32,053	30,656	5462	19,951	41,360
Aged 5 and over	40,620	10,145	20,737	60,504	26,022	1429	23,223	28,822
All age groups	31,999	4301	31,732	32,266	28,866	3369	28,657	29,075

TABLE 32 Estimated average cost (£) per patient from the bootstrap samples by age group and trial arm (excluding outliers)

	PCT				UC			
	Coefficient	SE	95% CI		Coefficient	SE	95% CI	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Under 5	26,532	2817	21,010	32,053	25,956	2739	20,589	31,324
Aged 5 and over	26,949	2224	22,591	31,307	26,022	1429	23,223	28,822
All age groups	26,633	1921	26,514	26,752	25,918	1788	25,807	26,028

TABLE 33 Estimated median IV antibiotic duration from the bootstrap samples by age group and trial arm

	PCT				UC			
	Coefficient	SE	95% CI		Coefficient	SE	95% CI	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Under 5	88.00	4.26	79.65	96.35	93.35	2.88	87.70	99.00
Aged 5 and over	103.02	6.62	90.05	115.99	111.85	4.11	103.80	119.90
All age groups	93.64	3.61	93.41	93.86	100.34	2.37	100.19	100.48

Our results show that PCT testing is associated with a higher cost and a slightly lower duration of IV antibiotic treatment (*Tables 34* and *35*, *Figure 7*).

Again, results are presented without outliers included in the bootstrap estimation (see *Table 35*, *Figure 8*).

Our results show that BATCH is associated with a higher cost and a slightly lower duration of IV antibiotic treatment. If outliers are excluded, the intervention presents a lower cost-effectiveness ratio pointing towards gains for the NHS if rolled out across more hospitals.

TABLE 34 Incremental cost-effectiveness ratio per IV duration hour avoided from the bootstrap samples

	Coefficient	SE	95% CI	
	(1)	(2)	(3)	(4)
Incremental costs (£)	3133.05	171.52	2795.82	3470.28
IV duration avoided (hours)	−6.70	0.13	6.44	6.96
ICER (Δcost/Δhour)	£467.62/IV hour avoided			

TABLE 35 Incremental cost-effectiveness ratio per IV duration hour avoided from the bootstrap samples (excluding outliers)

	Coefficient	SE	95% CI	
	(1)	(2)	(3)	(4)
Incremental costs (£)	715.59	80.81	557.02	874.17
IV duration hours avoided (hours)	−6.70	0.13	6.44	6.96
ICER (Δcost/Δhour)	£106.80/IV hour avoided			

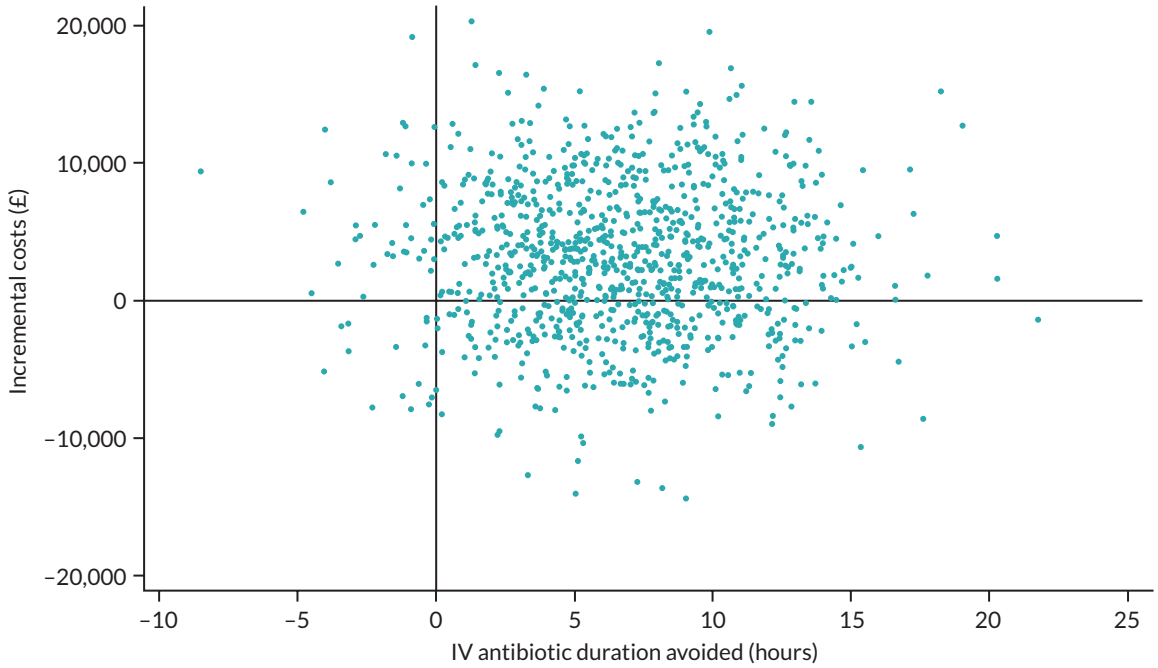

FIGURE 7 Cost-effectiveness plane comparing the intervention group to the control group.

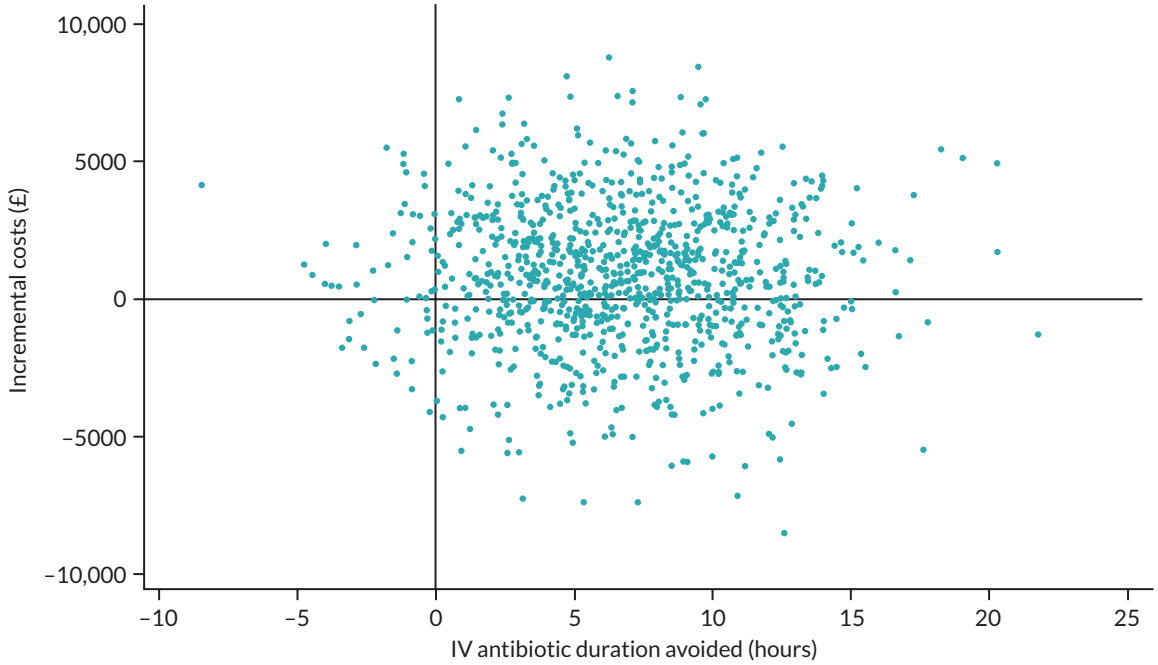

FIGURE 8 Cost-effectiveness plane comparing the intervention group to the control group (excluding outliers).

Sensitivity analysis: a complete-case analysis

In order to assess the robustness of the results presented so far, we performed a complete-case analysis (*Table 36*). Median IV antibiotic duration was shorter for the patients in the PCT arm than for the patients in the UC arm. Costs per patient also maintained the pattern observed in the previous analysis, higher in the PCT arm for all age groups, and for children aged 5 and over.

In this analysis, ICER is £6940 per hour of IV antibiotic duration, PCT is more expensive, but it is also more effective.

Tables 37 and *38* report the MICE estimates of the secondary outcome, CHU9D, from baseline to 28 days post randomisation. Results suggest that the PCT-guided treatment leads to an improved HRQoL as patients in the PCT group present higher CHU9D scores in all age groups (non-significant).

Table 39 reports the changes in the secondary outcome, CHU9D, from baseline to 28-day follow-up by trial arms. Results suggest that the PCT-guided treatment leads to an improved HRQoL as participants in the PCT group present higher CHU9D scores, but this difference was not significant. Parents for all children report an increased HRQoL of 0.007 from baseline to 28-day follow-up.

Productivity losses

Carers' income and work life are affected by their role. Participants in the trial were asked about the number of missed days at work, additional child-care needs, and days off school for the sick child. In order to account for those losses, we considered the number of hours people currently working had to take off work due to their caring role.

The pattern observed for productivity losses in both arms (*Table 40*) was higher in the PCT group during hospital stays. However, since discharge from hospital, family income losses were slightly higher in the PCT group, but days off school were lower in the PCT group. Additional child-care costs are not very relevant neither during hospital stays or after discharge.

TABLE 36 Results from a complete-case analysis

	PCT			UC		
	Median	**SD**	***N***	**Median**	**SD**	***N***
	(1)	**(2)**	**(3)**	**(4)**	**(5)**	**(6)**
IV antibiotic duration (hours)						
Under 5	80.00	136.99	418	86.00	109.16	400
Aged 5 and over	111.93	198.52	277	107.75	107.42	298
All age groups	93.10	165.74	695	93.60	108.77	698
Difference (Δhour)	−0.50					
	Mean	**SD**	***N***	**Mean**	**SD**	***N***
	(1)	**(2)**	**(3)**	**(4)**	**(5)**	**(6)**
Costs per participant (£)						
Under 5	26,531	57,346	418	30,656	108,918	400
Aged 5 and over	40,625	164,385	277	26,024	25,231	298
All age groups	32,148	113,006	695	28,678	84,069	698
Difference (Δcost)	£3470					

TABLE 37 Multiple-imputation estimates (20 sets of imputations) of CHU9D dimensions for parents of children at baseline and 28-day follow-up by treatment allocation

	PCT intervention				UC			
	Mean	SE	95% CI		Mean	SE	95% CI	
CHU9D dimensions	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Baseline	***For parents of children (all age groups)***							
Worried	2.308	0.055	2.198	2.417	2.312	0.063	2.186	2.439
Sad	2.568	0.057	2.455	2.681	2.565	0.055	2.455	2.675
Pain	2.609	0.049	2.512	2.707	2.632	0.049	2.534	2.730
Tired	3.526	0.056	3.414	3.638	3.607	0.055	3.497	3.717
Annoyed	2.506	0.055	2.397	2.615	2.535	0.063	2.409	2.661
School work	3.598	0.109	3.376	3.820	3.557	0.105	3.342	3.771
Sleep	2.444	0.047	2.351	2.537	2.385	0.045	2.295	2.474
Daily routine	3.380	0.060	3.261	3.500	3.409	0.058	3.295	3.523
Ability to join activities	3.906	0.050	3.807	4.004	3.923	0.056	3.812	4.033
Follow-up	***For parents of children (all age groups)***							
Worried	1.426	0.042	1.342	1.509	1.490	0.048	1.392	1.587
Sad	1.394	0.041	1.313	1.475	1.395	0.037	1.322	1.469
Pain	1.453	0.047	1.357	1.549	1.522	0.039	1.443	1.601
Tired	2.005	0.051	1.904	2.106	1.979	0.054	1.871	2.088
Annoyed	1.516	0.044	1.429	1.604	1.561	0.051	1.457	1.665
School work	1.683	0.070	1.541	1.826	1.727	0.078	1.569	1.885
Sleep	1.642	0.045	1.552	1.731	1.710	0.053	1.603	1.817
Daily routine	1.624	0.052	1.520	1.727	1.642	0.052	1.538	1.746
Ability to join activities	1.915	0.078	1.756	2.074	1.860	0.057	1.747	1.974

TABLE 38 Multiple-imputation estimates (20 sets of imputations) for CHU9D scores from baseline to 28-day follow-up by age group and trial arm

	PCT intervention				UC			
	Mean	SE	95% CI		Mean	SE	95% CI	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
For parents of children under 5								
Baseline	0.646	0.006	0.634	0.657	0.657	0.006	0.646	0.670
Follow-up	0.890	0.005	0.881	0.899	0.895	0.004	0.887	0.905
For parents of children aged 5 and over								
Baseline	0.611	0.008	0.594	0.627	0.593	0.008	0.577	0.609
Follow-up	0.846	0.009	0.829	0.864	0.827	0.008	0.812	0.843
All age groups								
Baseline	0.634	0.005	0.625	0.644	0.635	0.05	0.626	0.646
Follow-up	0.876	0.004	0.868	0.884	0.873	0.004	0.865	0.881

Note
The CHU9D index score was estimated using the preference weights.[30] MICE was employed to estimate the coefficients.

TABLE 39 Multiple-imputation estimates (20 sets of imputations) for changes in CHU9D scores from baseline to 28-day follow-up by age group and trial arm

	PCT				UC			
	Mean	SE	95% CI		Mean	SE	95% CI	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
For parents of children under 5	0.242	0.007	0.228	0.257	0.235	0.007	0.221	0.249
For parents of children aged 5 and over	0.233	0.010	0.213	0.252	0.226	0.011	0.205	0.247
For all parents	0.239	0.006	0.227	0.250	0.232	0.006	0.219	0.244

Note
The mean was estimated using MICE indicating the change of CHU9D from baseline to 28-day follow-up within each group.

TABLE 40 School or work missed days, all age groups, during hospital stay and since discharge, by trial arm

	PCT			UC			*t*-test
	Mean	95% CI	*N*	Mean	95% CI	*N*	*p*-value
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
During child's stay in hospital							
Days off school (child)	4.62	4.08 to 5.16	740	4.33	3.82 to 4.85	729	0.45
Days off work	6.50	5.78 to 7.21	722	6.17	5.54 to 6.81	707	0.51
After discharge from hospital (up to 28-day follow-up)							
Days off school (child)	2.87	2.50 to 3.24	709	3.30	2.87 to 3.73	696	0.14
Days off work	2.17	1.83 to 2.51	694	2.15	1.76 to 2.53	678	0.94

Discussion

The PCT test in itself is not very expensive (£14); nevertheless, it does contribute to a modest reduction in the number of hours of IV antibiotic administration. Results of the cost analysis of complete cases were also higher in the PCT arm for all age groups, and for children aged 5 and over. The intervention is not cost-effective as it is more expensive with no significant improvement in IV antibiotic duration, even though it resulted in a non-significant improvement in HRQoL. Productivity losses are similar in both arms. It should be noted that income losses of around £200 a child during hospital stay are significant for families.

Strengths and limitations

The analysis was undertaken following NICE guidance and used actual data on costs incurred in the intervention and comparator. We adopted a very conservative approach to the costs in the intervention, as other manufacturers might offer cheaper tests. We collected and reported the costs to the participants and their families, as recommended by NICE. Using the NHS and social care perspective or complete cases, the results obtained were always in the same direction that the intervention was more expensive than UC with negligible effects in terms of HRQoL.

Nevertheless, our results are robust with and without outliers, and also when a complete case-analysis was conducted: using a PCT test always contributed to reduce the duration of IV antibiotics.

The analysis has some weaknesses. As is common practice, we relied on self-reported data on health service use after discharge.[63,64] This may have been subject to recall bias. However, it should be noted that we have very detailed data about the use of medicines.

Fit with existing literature

Our analysis makes a significant addition to the literature on health economic analyses of PCT and IV antibiotic treatment for children, which, overall, remains scarce.

Chapter 5 Qualitative interviews with healthcare professionals and parents

Introduction

This chapter reports on the results of the qualitative interviews with HCPs and the parents of the child patients who took part in the trial. It is divided into three sections. Part 1 explores issues around the *acceptability and implementation* of the PCT test and algorithm in the trial from the perspective of HCPs. Part 2 explores *acceptability of the intervention* from the perspective of parents. Part 3 provides a qualitative evaluation of the *trial processes* from the perspectives of both HCPs and parents, to provide lessons learnt for future trials with hospitalised children.

Methods

A full description of the methods is provided in *Chapter 2*.

Preliminary analysis was led by the data, and themes also drew on topics from the interview guide, rather than being driven by a particular theory. However, for interpretation, we used the Consolidated Framework for Implementation Research (CFIR)[65] as a guide, in order to consider the way in which the intervention was implemented within the trial setting.

Qualitative analysis was carried out independently with no knowledge of the implementation outcome to avoid bias. Interviews and analysis were carried out by experienced qualitative researchers [data collection: Lucy Brookes-Howell (LB-H), Kim Smallman (KS) and Sarah Milosevic (SM); coding and double-coding: Lucy Brookes-Howell (LB-H), Sue Channon (SC) and Hayley Prout (HP)].

In this chapter, the term 'parent' is used to refer to the adult interviewed about the child patient. We did not seek to clarify the adult's relationship to the child during the interview, for example, with regards to parent, step-parent, carer or guardian. Therefore, we will use the term parent as a generic term. Illustrative quotes are presented in *Appendix 5* (*Tables 45–51*) and interviewer's minimal responses (yes, okay, I see, etc.) are removed for purposes of flow.

Results

Healthcare professionals interviews

This chapter draws on 29 interviews carried out with HCPs across eight sites in England and Wales, at different time points within the trial (18 relatively earlier in the trial between 2018 and 2019, 11 later in the trial 2020–2). Two of the interviews were group interviews, so we interviewed 33 HCPs in total. One of the HCP interviewees was also asked the (SWAP) interview questions so is also included within the SWAP (*Chapter 6*). In some of the interviews, a research nurse remained present. HCP roles included paediatric consultants, nurses/nurse specialists and pharmacists. Interviews were a mixture of face to face and remote.

Parent interviews

A total of 16 interviews were carried out with parents across six sites in England. Nine received the intervention and seven received UC. All parent interviews were carried out remotely and took place between 2019 and 2021. During one parent interview, the older child patient who had received the intervention wished to be present.

Detailed demographics are not given due to the smaller sample size, and because our analysis does not make distinctions between demographic characteristics, such as gender or age.

Part 1: acceptability of intervention to healthcare professionals

General overview

Part 1 explores issues around the acceptability and implementation of the PCT test and algorithm in the trial, from the perspective of HCPs. It looks at advantages and disadvantages of the PCT test, and barriers and facilitators to the implementation of the algorithm in the trial setting (see *Tables 45–47*). We then consider these findings in relation to the CFIR and make suggestions to enhance implementation of the PCT test and algorithm in the future.

Advantages of the procalcitonin test

Healthcare professionals talked about the intervention and its impact on decision-making around reviewing antibiotics (e.g. deciding when to switch from IV to oral or de-escalation) and stopping antibiotics (discontinuation), rather than the initiation of antibiotics. Most HCPs expressed reasoned views on the PCT test, presenting views on both the potential advantages and disadvantages of the test.

Healthcare professionals felt that the intervention could allow them to make a quicker and easier decision about antibiotic de-escalation or discontinuation. Many felt that the PCT test results could be powerful when combined with other 'tools', such as other test results, including CRP, the patients' clinical picture, and the patients' medical history. Some expressed the view that a series of PCT results might be more useful than a single result. Many felt that the PCT test compared favourably with CRP believing it was more specific and had less lag time. Some HCPs felt that the PCT test was more useful for some groups of patients than others, including postoperative patients, those with auto-inflammatory disease, and those with multiple pathologies (see *Chapter 6* for a more detailed discussion of the intervention and children with comorbidities).

Some HCPs felt that the intervention could give them more confidence in their management decision and help them provide patients with the right treatment more quickly. This would benefit the patient and parents as they would be discharged home more quickly, and would benefit the organisation, as quicker discharge of patients would help with hospital flow, and greater availability of hospital beds. Some HCPs felt that the intervention could be used to 'convince' prescribers to stop antibiotics, mindful of antibiotic stewardship.

To summarise, the advantages of the PCT test could be seen at different levels including: *Individual HCP level* (aiding HCP decision-making and increasing confidence), *Individual patient level* (receiving the 'right' treatment more quickly which could lead to shorter duration of hospitalisation), *Organisational level* (aid hospital flow) and *Societal level* (supporting AMS to reduce AMR).

Disadvantages of the procalcitonin test

As well as describing advantages of the intervention, HCPs also talked of some disadvantages to the intervention. Some HCPs felt that sometimes 'too' much information was not helpful. One HCP felt that some HCPs may have less faith in such tests generally, including CRP and PCT. HCPs felt that there was a lack of evidence on how well PCT works, and which scenarios it was not useful for. For example, some HCPs felt that the PCT test result was less useful for patients with abdominal infections and bone infections. Some also pointed out that the trial excluded certain groups of patients, for example, those with immune deficiencies and oncology patients, and therefore they could not know how useful the PCT test result would be with those patients.

Some HCPs expressed the view that the PCT test was expensive. However, some felt that the cost of the test was coming down, and that the cost of the test could potentially be recouped if the PCT test led to improved patient management.

There was a need to consider the context within which the HCPs were using the PCT test, and a need to consider the whole patient, rather than just the PCT test result in isolation. Some HCPs explained that they were managing a very sick cohort of patients, for whom further deterioration could be catastrophic (see also *Barriers to using the algorithm*).

To summarise, HCP views on the disadvantages of the test can be seen as having impact at many levels including: *Individual HCP level* (potentially confusing HCP decision-making and causing anxiety), *Individual patient level* (potential

catastrophe if there was further deterioration in the sick child patient), *Organisational level* (cost of test) and *Societal level* (balancing AMS to reduce AMR, with safe management of very sick cohort of children).

Barriers and facilitators to carrying out the procalcitonin blood test in the trial setting

The HCPs described the taking of blood for the PCT test as fitting in with their practice of taking bloods for monitoring of treatment response. There were some examples of extra bloods being taken, but these tended to be described as the exception to the norm. Some HCPs talked about salvaging remnant blood samples from routine blood tests to be able to do a true baseline PCT test. One HCP talked about difficulty in getting values in samples that had to be diluted, in cases where there was insufficient sample volume.

The time taken to get the PCT result was an important issue brought up by HCPs. Different HCPs, even within the same site, varied in their accounts and experiences in terms of the time taken to get the result. Some felt that within the trial, the turnaround for test results was quite slow, but others felt that the turnaround was fast, and some said the results were available 'within a few hours'. Within the infrastructure, the logistics and system developed for the test to be carried out varied (this is discussed further below, as it could then be a barrier to using the algorithm if the test result was not available when a decision had to be made). Some described that they had to take the sample to the lab for lab staff to perform, and in others they performed the test themselves in the lab. Slow turnaround with test result could be due to lack of staff, or the way that the lab was run (e.g. results not available on weekends, or after a certain time in the afternoon). Depending on their experiences within the trial, some felt that time taken to receive the result would improve if the test was widely rolled out and available on an automated sample platform used for routine blood tests. The time taken to receive the result could be seen as a barrier to use of the algorithm (see *Timeliness of PCT result*).

Barriers and facilitators to using the BATCH Algorithm to interpret the procalcitonin test results in trial setting

General overview

Healthcare professionals appeared to view the algorithm use as non-problematic when the algorithm aligned with a patient's clinical picture, for example, a patient was improving clinically and the PCT test showed PCT levels going down. In such cases, the algorithm might provide confirmation of their clinical assessment. HCPs described a number of facilitators and barriers to using the algorithm in the trial setting (see *Tables 48* and *T49*).

Facilitators to using the algorithm

Straightforward to follow, confidence and seeing good outcomes

Some HCPs showed enthusiasm about the intervention and found it was a useful tool in decision-making. They felt that the algorithm was straightforward to follow, and were happy to follow it, particularly after they had been doing the study for some time, and had seen positive outcomes of following the algorithm, which had in turn given them more confidence in using the algorithm. There appeared to be a process of self-efficacy for some HCPs. One HCP felt that their practice changed, regardless of whether a patient was in the trial arm. The trial gave them the confidence to make antibiotic decisions.

Many recalled that the algorithm had been revised by the trial team during the course of the trial and felt that this had simplified the algorithm for use (*Figure 3*). However, when the PCT provided contradictory information to what the HCP had expected this could be a barrier to its use (see *Barriers to using the algorithm*).

The Site Trial Team and developing exact nature of individual roles and responsibilities

Some HCPs talked about working out which specific individuals would be responsible for what, and how that evolved during the course of the trial. In one site, HCPs described themselves as being 'hands off' at first to encourage the clinical team to make management decisions, before realising that they needed to take responsibility themselves, and just give the clinical team the result and interpretation. Another HCP talked about taking personal responsibility for taking the sample and running the test so they can 'make sure it's done properly'.

The impact of specific individuals, for example, PIs or research nurses, within some sites as encouraging implementation was introduced by HCPs. HCPs often mentioned the crucial role of the research nurses. In those sites who had an IDs team, HCPs explained their important role. The input of the ID team seemed even more important where medical teams were less familiar with the PCT test, or the PCT result was not what they were expecting.

Communication of result/algorithm reminders within the site

A variety of ways were used to communicate the PCT test result to HCPs. It may have been put on the electronic patient record, e-mailed, phoned through or bleeped to the medical team. In one site, they described introducing a sticker with the result on it being placed in the patient's medical notes so HCPs could say what their management decision had been based on the PCT result. They also put the algorithm on a sheet which contained information on all of their trials, and 'plastered' the algorithm all over the doctor's office. One site wrote handover sheets in the notes on a Friday about what needed to happen over the weekend, including the suggestion to contact the ID team if a decision is needed to be made on a BATCH patient over the weekend.

The antibiotic stewardship agenda

Some HCPs talked about PCT being useful to address antibiotic prescribing 'just in case', which has wider implications for antibiotic stewardship. One HCP talked of PCT as an 'extra weapon' to convince prescribers to stop antibiotics, for example, if CRP is high/borderline. Another HCP talked of the PCT from a stewardship perspective, using it as 'back up' to stop antibiotics sooner. However, related to this, is the feeling from some HCPs that this must be balanced against the high risks to deterioration in this very sick cohort of children (see *Barriers to using the algorithm*). Some HCPs described their local setting as already 'very hot' on antibiotic usage. This may be due to microbiology/ID team ward rounds. In these settings, the 'added' value of the intervention may be perceived to be less by HCPs, as they believe they already carry out prudent antibiotic use.

Barriers to using the algorithm

Earliest version of algorithm was complicated

Some HCPs felt that the earlier version of the algorithm was complicated. They implied that there was some confusion and it was hard to follow. The revised version was simplified and received positively (see *Facilitators to using the algorithm* section).

Mismatch with clinical picture

Use of the algorithm appeared to be more challenging when the PCT test gave a result that did not align with the clinical picture. There appeared to be two main scenarios when this might happen.

Procalcitonin levels were high, but the child looked clinically well If a HCP assessed a child as clinically well, but the PCT levels were still high, HCPs may be reluctant to follow the algorithm, for example, reluctant to continue testing, and/or continue antibiotic use. HCPs may be reluctant to delay discharge due to a high PCT level if they felt that the child would 'usually' be discharged and able to go home. One HCP explained that HCPs may not wait to reach the final step on the algorithm to make their management decision if they can see that the PCT is getting lower. One HCP described a child's parents as being resistant to the child having 'more' tests or treatment as they felt that their child was well, based on their clinical picture. In this instance, the HCP recalled that the parent withdrew their child from the trial.

Procalcitonin levels were low, but the child looked clinically unwell If a HCP assessed a child as clinically unwell, but the PCT levels were low this may present a challenge to the HCP in using and following the algorithm. HCPs described the children in the BATCH trial as a very sick cohort of patients and there appeared to be a need to err on the side of caution regarding their management. Therefore, this implies that HCPs may continue to prescribe antibiotics if the algorithm suggested a different approach. There was a feeling that there was a need to consider complex patients, their past history, and the evolving situation of children's conditions. In situations where the algorithm and clinical judgement did not align, some described anxiety or nervousness over what to do, whereas others appeared to state quite clearly that they would follow their clinical judgement.

Risk–benefit analysis, worst-case scenarios and previous negative experiences

While some HCPs talked about antibiotic stewardship (see *Facilitators to using the algorithm* section), some also described the need to act within the context of the real-life setting with very ill children in intensive care. Some felt that they had to carry out a risk–benefit analysis to consider the worst-case scenario and err on the side of caution, for example, using antibiotics for longer. This may potentially be compounded by a negative experience or a 'tragedy' in the past which may influence HCPs antibiotic usage.

Wariness of algorithms and/or tests

Some HCPs recalled that the algorithm was open to be variably interpreted by those who may follow the spirit of it but not the exact letter of it, as the trial itself was a pragmatic trial. However, despite the pragmatic nature of the trial, some HCPs more openly expressed cynicism about following algorithms and protocols. Some talked of clinical medicine as not being 'black and white'. Some HCPs did not hold that view themselves, but described colleagues or other 'types' of HCPs who were resistant to using tests at all and preferred to follow their own judgement, and HCPs described some colleagues as not having faith in the test.

Lack of robust evidence

As mentioned above, some HCPs felt that there was a lack of robust evidence on how well PCT works, and which scenarios it was and was not useful for. Some HCPs appeared to be 'holding off' making a judgement about effectiveness of the PCT test to achieve the desired outcome until the trial results were reported. However, some HCPs felt that there was some good evidence around using PCT, albeit in different contexts, for example, with adult patients, with COVID patients, within different specialties. Some appeared to 'build' evidence through their own experiences during the trial, for example, which groups of patients the PCT test was more or less useful for.

Children under the care of other teams/specialities

Some HCPs described situations where they were aware that the algorithm was not being followed as well for some children who were under the care of other HCPs who were not paediatricians, for example, orthopaedics, ear, nose and throat (ENT), or surgical team. They felt that in these situations, the HCPs may be more used to dealing with adult patients and did not want to 'tamper too much with antibiotics' of the patients.

The time point at which HCPs saw the patient also played an important role in the extent to which HCPs could use the algorithm. Some HCPs explained that an antibiotic decision may have already been made when they see the patient. Another HCP explained that while not on duty, other colleagues not involved in the trial may make decisions on a patient without discussing them, suggesting the algorithm may not then necessarily be followed for that patient. One HCP talked of the challenge of engaging trainees with the trial, who are then rotated on to another hospital, and another group of trainees need to be engaged again.

Timeliness of PCT result

Some HCPs described not receiving the test result in time for the ward round, therefore meaning that a decision about antibiotics may have been made before the HCP had seen the PCT result. On such occasions, it appeared that the algorithm could not therefore be reviewed or adhered to.

Procalcitonin result not showing on computer system

The method of reporting the PCT test results varied between sites. Some HCPs observed that the results were available to be seen on their computer screen, so this did not appear to be a barrier for some. One HCP explained that the PCT test results were not automatically pulled through into their computer system, and they had to go hunting for it.

Forgetting or not understanding algorithm earlier in the trial

Some HCPs described the beginning of the trial and felt that HCPs were forgetting and not understanding the algorithm at first, but that this improved during the course of the trial.

Healthcare professionals' views on intervention recipients: parents and child patients

Generally, HCPs did not appear to report parental pressure for antibiotics as having a big impact on the use of the PCT test and algorithm. One HCP felt that pressure for antibiotics was less of an issue in hospitals, but more so with GPs in

the primary care setting. Another surmised that there may potentially be pressure, but while in a trial setting, research nurses were able to take the time to communicate antibiotic decision-making with parents. They felt that this careful communication was something that would take time in a real-life setting. The extent to which HCPs discussed PCT test results and algorithm with parents varied.

Implementation of the intervention with the trial

The findings above can be mapped against aspects of the CFIR.[65] This allows us to describe the factors encountered during implementation of the intervention within the trial setting and make suggestions around strategies to address these (*Table 41*).

TABLE 41 Mapping BATCH findings on to CFIR domains to inform implementation

CFIR domain	CFIR construct	Summary of findings
Innovation; PCT test and algorithm	Evidence base	Limited evidence to support intervention although some evidence from other settings (e.g. adult patients, COVID patients)
	Complexity	Test: Blood sample generally taken with routine bloods using IV lines Algorithm: Views varied with many feeling algorithm straightforward but some questioning thresholds. HCPs positively recalled that algorithm was simplified during the trial
	Relative advantage	PCT useful when combined with other factors (e.g. clinical picture, history, other tests) PCT compared favourably to CRP and contributed to quick decision on appropriate treatment benefiting patients and hospital flow
Individuals; HCPs	Innovation deliverers: capability	Intervention could give confidence in management decision-making. However, if intervention gave contradictory information to 'expected' management decision could create anxiety/nervousness. For some, confidence improved over time as they saw positive outcomes
	Innovation deliverers: motivation	Some HCPs positive and felt intervention was useful tool in decision-making. Some disappointed if patients randomised to UC as extra PCT information was useful. Some demonstrated less enthusiasm/more resistance to use of intervention in decision-making
	Innovation recipients	Child patients received intervention with consent of parents/carers. HCPs felt parents did not want 'extra' blood taken purely for trial purposes; Parents did not want intervention to cause deviation from usual management
	Implementation leads	Impact of individuals in encouraging implementation recognised, particularly research nurses
Inner setting	Physical infrastructure	The positioning of the machine may have an impact on accessible and timely results
	Information technology infrastructure	For some, current computer data system did not pull PCT result through automatically
	Work infrastructure	Patient flow through hospital: Antibiotic decision may have already been made by time of seeing patient
	Relational connections and communications	Handing over to colleagues, or from other specialties (e.g. surgical), may mean management decisions then made by HCPs with less awareness of intervention ID team: input from ID team helpful in facilitating decisions based on the intervention
	Compatibility	PCT blood sample generally fitted in with routine blood taking. However, processes for carrying out the test and returning results varied. Test result generally not available in evenings or weekends and some HCPs described PCT result not being available in time to make a decision. This may be different for other tests, for example, CRP, which are routinely available. However, some HCPs felt that the test result was available relatively quickly
	Available resources	Staff to run test: For some sites available resource, including lab staff, was a challenge in terms of running test. Some HCPs described taking samples to lab or offering to take personal responsibility for the running of the test. Research nurses were valuable in implementing intervention and communication with parents

TABLE 41 Mapping BATCH findings on to CFIR domains to inform implementation (*continued*)

CFIR domain	CFIR construct	Summary of findings
Outer setting	Local attitudes	Beliefs and values: Some HCPs described making antibiotic decisions in the context of the potential catastrophic outcome if children deteriorated further. One described a heightened paranoia. However, others felt that the intervention could be back up to address antibiotic prescribing 'just in case'
	Local conditions	Regional prescribing patterns: Relative 'value' of intervention may depend on whether HCPs already have strong AMS programme at that site
	Critical incidents	COVID meant that some HCPs were becoming more familiar with PCT as it was used with adult COVID patients and there was some crossover of staff
	External pressures	AMS agenda balanced with the real-life practice of protecting very sick children in this healthcare setting

Many of the factors influencing implementation concern the *inner setting*, for example, availability of staff to run test for timely result, and communication of the test result, despite the extra resources (time of research nurses and equipment) provided for the Trial. A combination of *individual* HCP attitudes, *local attitudes* and *external pressures* can be seen as influencing implementation as awareness of antibiotic stewardship issues met the need to care for a very sick child in a real-life, real-time critical setting. *Individual* HCPs' confidence and motivation to use the intervention are influenced by the current limited *evidence base* for the intervention. By looking at these factors, we can suggest some considerations for future implementation of the PCT test and algorithm.

Considerations for future implementation based on healthcare professional interviews

Considerations for implementation in the future are based on direct suggestions from HCPs, and our own interpretation of the findings above. They include:

Algorithm content: Some HCPs suggested the possibility of stopping antibiotics earlier. The algorithm and its interpretation could be relaxed to fit with the real-life clinical setting.

Testing process: The timing of the turnaround of the test could be quicker and the process could be streamlined. Test results could also be available later in the day/evening, and on weekends. One suggestion might be that doctors do bloods earlier in the day to allow the tests to be run in daylight hours.

Communicating PCT results within sites – computer systems: In one site, the current computer data system did not pull through the PCT result automatically. It would be documented in a microbiology notation system, but they would have to 'go looking for it'. However, in another site HCPs could see the results on the screen, so this varied from site to site. Test result should be added to the system, so it is pulled through automatically, for example, Careflow, Meditech.

Communicating PCT results within sites – physical reminders: Handover sheets could be used to ensure that colleagues continue to use the PCT result and algorithm to guide their decision. Laminated sheets of the algorithm could be available both as notices in the doctors' office, and on a lanyard. PCT results stickers could be stuck in patients' notes to remind HCPs to use them in their decision-making.

Procalcitonin champions: The ID and AMS team could also be used to reinforce decision-making along the algorithm guidance until HCPs gain more experience and confidence. PCT champions could be identified at each site who could drive the implementation of the algorithm.

Education for HCPs: There should be robust evidence-based education delivered on the PCT thresholds and their interpretation, and on when to use the test (e.g. how often). The education should be multidisciplinary across teams and roles including clinicians, nurses and pharmacists, and any other HCP involved in making antibiotic decisions about the patients including different specialties, for example, general surgery and oncology. The education should be ongoing

in nature to sustain change over time and avoid HCPs returning to 'old habits', and to address the rotation of doctors in the NHS. Different education packages could be tailored for more experienced consultants who may be resistant to changing established practices.

Cost: Although not a consideration within the trial setting, the cost of the test may affect implementation in the future. Some HCPs described the PCT test as expensive but felt that if evidence showed that PCT was effective, the cost of PCT would not be a barrier to implementation in the future. This was because the costs were coming down, and implied that costs could be reimbursed or recouped if it impacted on clinical decision-making (possibly by reducing antibiotic usage).

Part 2: acceptability of intervention to parents

Part 2 of this chapter explores acceptability of the intervention from the perspective of parents (*Table 50*).

Contextual factors: parental concern over their child's condition

Parents gave an account of the events and experiences they had encountered before reaching the point at which they entered the trial. This often involved encounters with other HCPs and/or other healthcare settings, for example, GPs or other hospital sites, before transferring to the hospital in which they entered the trial. Their child was unwell or in pain, and there had been, or still was, uncertainty around what was going to happen next. It is important to understand the context in which parents and children were first introduced to the trial.

Acceptability of intervention

Acceptability of the intervention from the perspective of parents focused on two main themes: concern over extra blood being taken, and deviation from usual practice.

Overwhelmingly, parents described their initial concern over the potential need for extra blood to be taken for the purposes of the trial, and the PCT test. They felt that their child had been through enough and wished to minimise the trauma of extra blood tests. However, most parents said that their child had not needed to have extra blood taken just for the purposes of the trial, and that IV lines were used. Occasionally, a parent did recall that a needle had to be used.

Some parents also expressed concern that taking part in the trial and/or receiving the intervention might mean deviation from the usual management their child would receive, if they had not been in the trial. Some felt that it could result in a longer recovery time, a longer duration in hospital, or that there might be a lengthy delay while waiting for test results. However, generally they did not feel that the trial had had a negative impact on their child's management. Some described feeling reassured that the HCP's clinical judgement was still the overriding factor in their child's treatment decision.

Recall of intervention

Generally, parents recalled their child receiving blood tests during their hospital stay. The parents' recall of the types and purpose of the blood tests varied, as did the amount of communication with HCPs before, during, and after these blood tests. Some parents volunteered, unprompted by the interviewer, explanations about why the blood tests were taken. Some were told more about the tests, and some were told once they had the results. Some parents said they may have been told but forgotten. Some parents could not recall the specific name of the PCT test, which may reflect recall bias as the parents may have forgotten given that the interviews took place a considerable time after the child's hospitalised episode. In addition, the parents had experienced a highly stressful situation with a very ill child, interactions with multiple HCPs, and a myriad of investigations, tests and checks which may have affected recall. While some parents did not recall a biomarker by name, some talked at length about blood tests being used to check for infections and some talked about infection markers being high.

Of those who recalled the biomarker or infection markers being checked, parents felt that it might provide information on; the 'best' antibiotic for that type of infection (which would allow better targeting of antibiotic type for optimum treatment), early indication for antibiotics (allowing for targeted antibiotic regime), reduce the length of time on

antibiotics, reduce the duration of the time on the 'stronger' antibiotics, provide information on when to stop antibiotics, and/or provide reassurance that the child was ready for discharge from hospital.

Parents' views on the antibiotic management of their child during the trial

Parents tended to recall and often described in detail what we can call their child's 'antibiotic timeline' including duration of antibiotic course, how many times a day antibiotics were administered, combinations, switches and often even days of the week that changes occurred. Parents clearly recalled their child being given IV antibiotics, sometimes administered immediately, while waiting for further information, for example, test results/investigations. Some parents felt they saw a quick improvement for their child once they had started IV antibiotics. Parents described their experience of their child on IV lines (cannulas and catheters). Some found them 'annoying' or 'horrible', for some the needle kept coming out, but others did not report the same concerns about the IV lines.

Communication around the decision to switch from IV antibiotics to oral was varied. One parent felt they were not involved and were frustrated with the confusing messages they were given from different doctors. One parent felt that they needed more information about 'strong' antibiotics, given how small their child was. However, on the other hand, another parent felt that the information they received was very clear, and said after the bloods were taken they were told about the change in the infection indicators. Parents who talked about the switch from IV to oral antibiotics described it as being done because their child was improving, based on test results, and one also recalled the switch coinciding with problems with the cannula becoming dislodged.

Some parents appeared to make a link between oral antibiotics and their child being ready or starting to be ready to go home. However, two parents described how their children left the hospital to go home but continued IV antibiotics. One parent talked about the oral antibiotics being more 'familiar'. One parent expressed a concern that oral antibiotics were not going to be as effective and that the child's condition might deteriorate as a result of the switch. However, they felt reassured by the HCPs that this was not the case. Some parents described that oral antibiotics gave their child upset tummy and diarrhoea or thrush, and mentioned issues with trying to get their child to take oral antibiotics at home.

Antibiotic resistance

Some parents initiated talk of antibiotic resistance (see also *Parents' reasons for deciding to take part (or not)*). One parent was concerned about the amount of antibiotics and another patient briefly acknowledged the notion of resistance as a risk associated with antibiotics. One older patient who was present during the interview with their parent also introduced the issue of antibiotic resistance and demonstrated knowledge in this area.

Considerations for future Implementation based on parent interviews

Based on the experiences of parents within the trial, we can make some considerations for implementation in the future.

If the PCT test were to be used in the future, it should be incorporated within the routine blood taking for the child, rather than as an additional sample, to minimise trauma for the child. IV lines could be used whenever possible, as they appear to be preferable to the use of needles for blood taking. HCPs could reassure parents that while the PCT test result provides additional information, it is part of a series of tools which are used to guide their clinical decision-making process. HCPs could check with parents the extent to which they want to be involved in communication of information around the reasons for reviewing antibiotics, for example, the reason for switching from IV to oral antibiotics. Clearly, while shared decision-making and informed consent will need to be maintained by HCPs with parents, the extent to which parents wish to receive updates on series of blood tests may vary, depending on the parent. General information on the tests routinely carried out during such episodes and information on the 'strong' antibiotics could be provided to parents. In the future, it would be useful to consider to what extent is it helpful or necessary for HCPs to explain the exact purposes/names of every test and for parents to recall this information.

Part 3: evaluation of trial processes

Part 3 provides a qualitative evaluation of the trial processes to provide lessons learnt for future trials with children in hospital, both on wards and in intensive care (*Table 51*).

Recruitment and consent

Identifying potential participants

Potential participants were identified by HCPs, for example, consultants who were engaged with the trial, who would then inform the research nurse, or the research nurse may attend meetings and find out about potential participants there. If relevant, the research nurse may check with the ward nurse or home care team whether it would be appropriate to approach the parent. The research nurse would then typically approach the parents, introduce the trial, and if appropriate, leave information with the parents for them to read in their own time. The research nurse would then come back, discuss the information and any questions with the parents, and the parent(s) would provide consent if they wish. There was a model of assent for older children available.

Parents' reasons for deciding to take part (or not)

During parent interviews, parents gave a range of reasons for agreeing to take part in the trial. Many of the reasons related to altruism and doing something to help others. Some parents talked of the importance of research for the future, and one in particular talked of the need to base care on research (i.e. contributing to knowledge to build evidence-based care). Some parents more specifically talked about the need for the research in relation to combatting antibiotic resistance. HCPs felt that sometimes parents made up their mind to participate quickly, which was confirmed by some parents.

Healthcare professionals felt that some parents, however, are just not interested in research and could tell that some parents would not want to take part. One HCP appeared to reflect that you could not always make assumptions though, as they had experienced some parents agreeing to participate at a time when the HCP had thought they might not. One HCP felt that they had not got a very high decline rate which is good for a study that involves taking a blood sample. A small number of HCPs observed that parents are less likely to say no if a consultant introduces the research.

Parents' concerns when deciding to take part

Healthcare professionals reported that in their experience, parents were generally quite happy with the idea of the trial but were worried about extra blood being taken from their child, and some worried that antibiotics might be stopped early. This matches the strong finding from the parent interviews, where parents spoke about their concern about extra blood being taken from their child for the purposes of the trial. Some said that they would not have wanted to take part in the trial if extra blood had been taken (but that it had been managed via routine bloods as discussed above). HCPs described that they rarely needed to take extra blood, but had to inform parents of the possibility that they might have to (see also *Trial materials*).

The role of research nurses in communication and timing of approach

During parent interviews, parents recalled research nurses approaching them to talk about the trial and leaving them with written material. The research nurses would leave and come back later having given the parent time to read and consider. A small number mentioned that they had not had time to read the leaflet when the research nurse came back. Some parents implied that they did not need time to consider. Parents appeared to feel they had plenty of opportunities to ask questions. Some parents felt that the timing was appropriate and did not recall feeling pressure to participate. A smaller number of parents implied that they felt they were approached quite early in their stay but stressed that they still felt it was handled sensitively. Some of these felt any earlier would have been too early. During the HCP interviews, HCPs were also aware that research nurses choosing the 'right' time to approach parents was important. They were aware of approaching at the appropriate time, but not missing the window of opportunity, before the child was due to stop IV antibiotics. One HCP explained that explanations about the trial refined over time, once HCPs got used to the study.

Trial materials

Leaflet/participant information sheet

During HCP interviews, some HCPs talked about the need to consent parents to the possibility of taking extra blood, even though in reality it did not tend to happen. One HCP felt that the information in the PIS regarding this might put parents off. HCPs at one site felt that it would have been helpful to have the trial materials translated into a different language (e.g. Urdu). They explained that they had used interpreters to help during discussions with parents. Another HCP felt that language and cultural barriers may have led to a misunderstanding from some parents who did not want their child to be used as a guinea pig, possibly implying that they associated research with 'experimentation'.

During parent interviews, comments about the 'leaflet' were generally positive, 'very informative' and 'it explained everything'. One parent recalled their partner still seeking reassurance about risk of infection from having blood taken and whether this was fully covered in the leaflet. Another parent recalled that they sought reassurance that the trial would not involve a change in their child's care which might delay their recovery.

Consent form

Similarly, those parents who talked about the consent form tended to be positive. Some felt that the consent form was broken down well and was clear. For some, precise details of the consent form were not necessarily recalled. Another felt it a bit long, and another felt that there was excessive paperwork generally.

Questionnaires/follow-ups

With regards to follow-ups and questionnaires, one HCP volunteered that they were struggling with follow-ups. They felt that by the time of the 28-day follow-up, the parent may be back into their routine of work and school, so it was a challenge to get through to them on the telephone. They found the return rate for posting the questionnaire varied; however, they reflected that this was a global problem, and not necessarily related specifically to the trial. Some parents found that the 'questionnaire' was aimed at older children (e.g. children who attend nursery/school), and some of the questions were not as applicable for their younger child, which 'threw' them, but they answered the questions as best they could.

Posters

Most parents did not mention or recall seeing posters about the trial at the hospital sites. However, one parent recalled there being posters at the beds about the trial, and another remembers there being a poster in their child's hospital room relating to overuse of antibiotics. It is possible that the latter was a generic poster and did not specifically relate to the trial.

Contamination and usual behaviour

In HCP interviews, HCPs explained that PCT was not used as standard with patients outside of the trial in UC. Many HCPs did not feel that their practice had changed due to being part of the trial, although one HCP explained that their awareness of how they treat infections had increased, just by being part of the study. However, some HCPs reported an important change had occurred during the course of the trial as a result of COVID-19. Adult teams had started using PCT in COVID-19 patients in intensive care, and there had been some crossover with paediatric intensive care doctors covering adults. They felt that some staff might be becoming more familiar with PCT, and while it was still not routine practice, there had been some occasions when staff had ordered a PCT test for patients who were not in the trial. Another HCP described that PCT had been ordered on 'a couple of occasions' for children in the control arm of the trial and the PI had intervened.

Randomisation and equipoise

Parents largely appeared to be aware that they had been allocated to the trial arm through a process of randomisation, some mentioning computer-generated randomisation. Some parents appeared to conceptualise the control arm as 'not being in the trial'. During parent interviews, some parents, when asked to think back, expressed that they had a preference to be in the intervention arm. But those parents who did express a preference for the intervention arm also felt that it would not have mattered if their child had been in the control arm as the PCT test would not have had an impact on duration of stay, the trial would not affect their child's care, and they would still be managed 'as it should be' based on professional judgement. HCPs appeared to be aware of the need for equipoise and randomisation of

patients for research purposes. However, HCPs often mentioned they, or colleagues, felt disappointed if patients were randomised to the UC arm as the extra information was useful.

Suggestions for future trial design

We can offer some suggestions to consider in future trial design with children in such settings. These suggestions are not necessarily directly offered by HCPs themselves but are our interpretations based on the findings above and include:

- The timing of the approach at which trial information is given to parents must be handled sensitively and the appropriate time will vary from parent to parent. Research nurses could check with ward nurses who may be able to provide further insight on whether it is an appropriate time.
- It is important to consider the role of the HCP who first introduces the trial to parents. One HCP surmised that parents are less likely to say no to participating in the trial if a consultant introduces the research. While this may be beneficial to the study, it is important that parents do not feel coerced into participating and that they have time alone to consider participation and discuss the trial with a different HCP, for example, research nurse.
- While it is important to inform and consent parents regarding the possibility of taking extra blood (for a trial involving a blood sample) it may be useful to provide information in the PIS about how often this can be taken from routine bloods rather than the need for extra blood. A figure could be taken from a trial, such as BATCH and presented in the PIS which may reassure some parents who would otherwise have declined participation.
- Some parents appeared to associate the 'active' part of the intervention arm as being 'in' the trial, and their use of language implied that they did not see the control arm as being 'in' the trial in the same way. It may be important to consider reiterating with parents the very valuable role they are playing while being in the control arm.
- It may be important to budget and plan both in advance, and make provisions if the need arises during the trial, to consider translating trial materials into different languages. It may be beneficial to work with PPI representatives at each site to consider which languages might be useful, and also to be sensitive to any cultural beliefs around research and trials which may be held by potential participants in that region.
- In order to warn HCPs about possible contamination between trial arms, warning flashes could be triggered by the computer system if trying to order a test which is part of the intervention.
- Guidance could be provided to parents on completing questionnaires if questions are not applicable.
- Follow-up calls could be made outside of working hours. Although not directly suggested by HCPs, if phone calls and posting questionnaires are not successful, it may be useful to consider an alternative method, such as e-mailing questionnaires.

Limitations of the study

The parent interviews were carried out some time after the child's hospitalised episode so there may be some recall bias. However, the emotions and memories related to such a significant event will remain with parents and are still very valuable at this time point. The issues that 'stick' in the parents' memory may be the most important to them.

The interview study has a relatively small sample size, particularly for the second phase of HCP interviews. We acknowledge that there was a challenge in recruiting interviewees. We can surmise that this may be due to the rotation of staff who had worked on the trial and moved on to other posts, no longer available for interview, the longer duration of the trial, and competing pressures on staff generally, exacerbated due to COVID-19. We believe that these challenges are not unique to this trial. Furthermore, HCPs who agreed to interview may be those naturally more interested in research, and more specifically in the intervention. However, if that was the case, we found that interviewees still provided extensive data on the disadvantages of the intervention and barriers to implementation.

Summary

We have reported on issues surrounding acceptability and implementation of the intervention and trial processes from the perspective of HCPs and parents. From this, we have made a series of suggestions to address implementation of the PCT test and algorithm in the future, and factors which may be considered when running future trials with children in this setting.

Chapter 6 Multiple long-term conditions (comorbidities) study within a project

A substudy embedded into the trial examined the differential effect of the intervention in children with multiple long-term conditions, referred to as comorbidities in the rest of the chapter.

Quantitative component

Methods

We described the frequency and percentage of the cohort with different types and numbers of comorbidities in *Chapter 3*.

The primary outcome of the comorbidities SWAP was duration of IV antibiotic treatment, and secondary outcomes were the composite safety outcome and adherence to the PCT algorithm, as defined in *Chapter 2*. All participants remained in the trial arm assigned by randomisation in the main trial, regardless of protocol deviations or non-adherence, and were included in the analysis if outcome and comorbidity data were available. Less than 2% of patients in each arm were missing data on comorbidities.

For the primary analysis, we fitted a Cox PH model with duration of IV antibiotic treatment as dependent variable. Patients were classified into three comorbidity subgroups (no comorbidity, single comorbidity or multiple comorbidities). For secondary analysis of the safety composite outcome, we used logistic regression, with the same subgroups. The procedure for subgroup analyses is described in *Chapter 2*. It was not planned to perform secondary analysis of the composite safety outcome in this substudy if the primary BATCH analysis found that the intervention is inferior to standard care. The third outcome is adherence, which is only defined in the PCT arm. Instead of a subgroup analysis (for interaction), we therefore tested whether adherence was associated with comorbidity category within the PCT arm.

As an additional exploratory analysis, we plotted post-intervention PCT trajectories, stratified by subgroup. We also explored the influence of respiratory comorbidities by further subdividing the comorbidity subgroups.

Results

There was no evidence of differences between comorbidity subgroups in the treatment effect on IV antibiotic duration or safety (*Table 42*). Comorbidity category not only predicted whether PCT results were considered (clinician behaviour) but also whether they were available in the first place (trial conduct) (*Table 43*). *Figure 9* shows adherence steps summarised by comorbidity category.

TABLE 42 Comorbidities substudy, subgroup analyses

Outcome	Subgroups	*n*	LRT X^2 (df)
IV antibiotic duration[a]	Comorbidities: none/single/multiple	1892	4.43 (2)[c]
Safety composite[b]	Comorbidities: none/single/multiple	1803	1.79 (2)[c]

df, degrees of freedom.
a Analysis method: Cox regression.
b Analysis method: logistic regression.
c Interaction tests by model comparison: $p > 0.05$.

Note
Covariates in all models: centre as a random effect and age as a fixed effect.

TABLE 43 Comorbidities substudy, adherence outcomes

Step	Frequency	*N*	LRT X^2 (df)
1. PCT available…	…at all clinical reviews	937	7.34 (2)*
	…at any clinical review	937	9.80 (2)*
	…at first clinical review	938	8.10 (2)*
2. PCT considered…	…at all clinical reviews	928	8.67 (2)*
	…at any clinical review	918	5.21 (2)
	…at first clinical review	929	4.29 (2)
3. Algorithm adhered to…	…at all clinical reviews	929	15.87 (2)*
	…at any clinical review	912	7.48 (2)*
	…at first clinical review	929	6.49 (2)*

df, degrees of freedom.

Note
Analysis method: logistic regression. Model comparison with/without main effect for comorbidity category: * $p < 0.05$, without adjustment for multiple testing. Covariates in all models: centre as a random effect and age as a fixed effect.

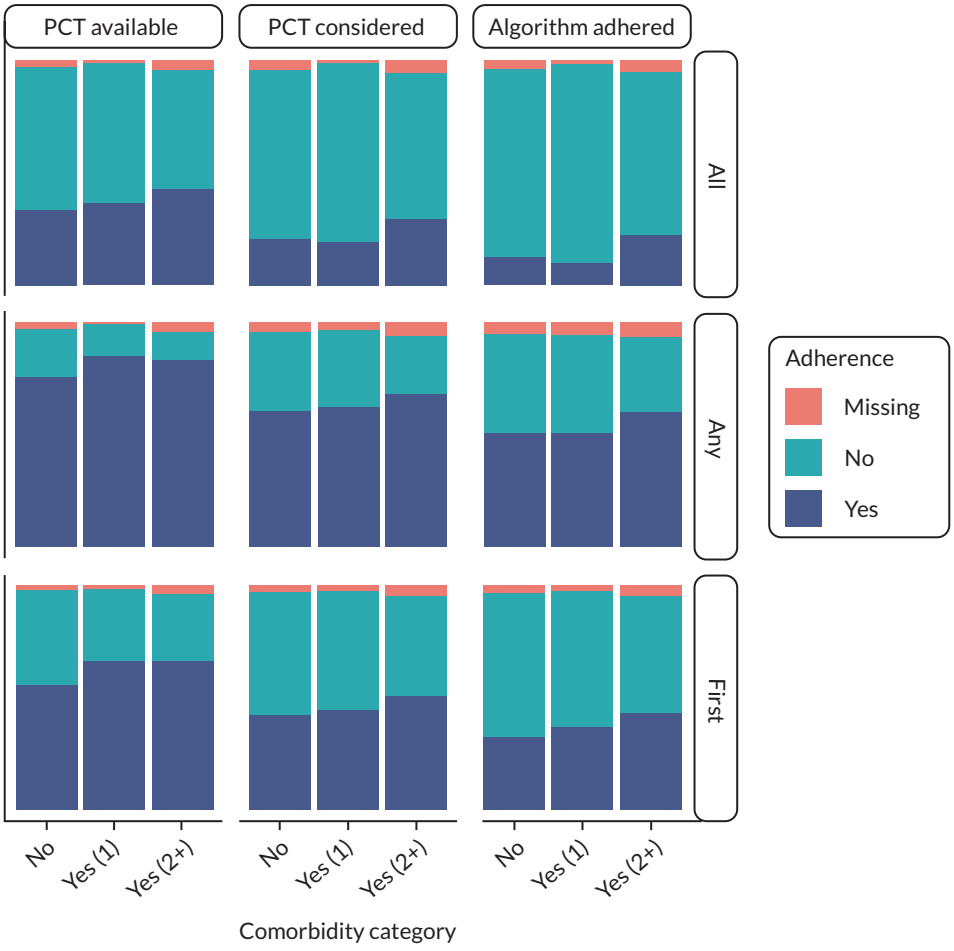

FIGURE 9 Adherence steps summarised by comorbidity category.

Qualitative component

Aims

The main aims of the qualitative interviews were to explore the views of HCPs and parents towards the influence of comorbidities on management decisions, and the influence of comorbidities on decisions around trial participation (particularly from the perspective of parents) and inclusion (from perspective of HCPs).

Methods

An interview topic guide was developed in discussion with the trial team, based on the main trial qualitative study, and refined to include the new focus on comorbidity. All interviews were conducted by an experienced qualitative researcher Josie Henley (JH). Sampling was pragmatic and we considered maximum variation across site, as well as other variables where possible including role (for HCPs).

Interviews were audio-recorded, transcribed and de-identified. Thematic analysis was carried out by experienced qualitative researchers (LB-H and SC) in discussion with the interviewer (JH) to identify key patterns in the data.[66] This consisted of a series of steps: familiarisation with data, generating initial codes, and searching, reviewing, and defining themes. Themes were identified that related to the objectives of the research, while also allowing for any new, unpredicted themes generated by interviewees themselves to be identified. During analysis, the researcher also looked for contradictory data as points of contrast, as well as similarities. Qualitative coding software, NVivo,[45] was used to manage the data. A thematic coding framework was developed and discussed by the qualitative researchers to reflect upon themes. Illustrative quotes are used and interviewer's minimal responses (yes, okay, ah, etc.) are removed for purposes of flow.

Results

Description of sample

This chapter draws on 10 in-depth qualitative interviews carried out for the BATCH SWAP (seven HCPs) – one of whom was also asked interview questions for the main trial interview study – and three parents of children with comorbidities who were recruited in the trial.

Detailed demographics of interviewees are not given due to the small sample and to minimise jigsaw identification. However, for the parent interviews, we can describe the comorbidity relating to the three child patients as genetic (neurological and musculoskeletal) and relating to a blood disorder. The arm of the trial and site was not relevant for this analysis as we wished to gather parental views on antibiotic use generally in relation to comorbidity, and impact of comorbidity on participating in trials. For HCP interviews, roles included consultants and research nurses, and HCPs from four sites were included. HCP interviews were carried out August–October 2022, and parent interviews August–November 2022. Parents are referred to using anonymised identification codes (PID A, B, C) and HCPs anonymised identification numbers.

Themes

A thematic coding framework was developed and data were coded in NVivo version 12[45] relating to the overall themes of:

Healthcare professional: HCP's background, views on PCT test, views on algorithm, influence of comorbidities, communication, contamination or changes to practice, trial processes.

Parents: before hospitalisation, during hospitalisation, after hospitalisation, influence of comorbidity, impact on parent, views on PCT test and algorithm, trial processes, influence of COVID-19, other.

Subthemes were identified and more detailed analysis was carried out at the interpretation stage. Results relating specifically to views on the impact of comorbidities on management and on participation in the trial are presented here.

Parent views on impact of comorbidity on management

Effect of comorbidity on child's problem presentation

We hypothesised that a child's presentation at hospital and management (including antibiotic duration) of suspected or confirmed bacterial infection may differ as a result of the child's comorbidity. Specialist knowledge or equipment at home may allow parents to make an 'informed' decision regarding presentation to hospital. For example, patient PID B had a cough and the parent had them checked by their local team who said the child had 'some sort of virus' and advised taking the child home and keeping an eye on them. At the child's home, they had a ventilator and other equipment so that they could check his 'sats' (oxygen saturation levels) which prompted them to take him to hospital (PID B). Alternatively, the child may present at hospital due to an issue relating to their comorbidity in addition to the infection managed within the trial. For example, it appeared that patient PID A initially presented at hospital with a physical injury relating to their comorbidity but was then transferred and treated for a chest infection in addition to the physical injury.

However, it does not necessarily follow that a child having comorbidities eases their admission to hospital. The parents of patient PID C accessed support via 111 during the night and attempted to arrange a GP appointment in the morning rather than presenting directly at A&E. However, on speaking to a nurse at the GP surgery, they were encouraged to present at A&E. This parent then described a pre-existing link with a team related to their child's comorbidity, signalling a level of awareness and experience in relation to healthcare encounters:

> *At that point I had jumped in the shower, got [child] dressed and took [child] straight to A&E and I phoned my haematologist as well just to let them know because [child's] got a [blood related condition] so I phoned them just to give them the heads up that [child] was going over to A&E and [child] would probably need treatment, just to make them aware.*
>
> *PID C*

Parents' general assessment of child's 'wellness'

When looking for signs of improvement, parents may assess their child's recovery from infection in relation to what is 'well' for them personally, taking into account their comorbidity. For example,

> *[child] is you know [child] is well at the moment so yes when I say [child's] fully recovered [child's] fully recovered from what ~[child] had you know back to [child's] baseline which is good.'*
>
> *PID A*

and

> *[child's] brilliant as [child] can be. [Child's] at her best now anyway for now.*
>
> *PID B*

Impact of comorbidity on child's ability to 'fight' infection

Some parents explained that their child's comorbidity meant that they had to be more careful if they get coughs and colds due to their 'lowered immune system', meaning they needed more support to fight an infection.

> *[child] has a genetic condition anyway so you have to be a little bit careful if [child] gets unwell with colds and coughs and things ... [child's] not necessarily more likely to pick them up it's just that [child] can't cope as well with them so [child's] sort of vulnerable to the effects … So if [child] does catch anything viral or bacterial in [child's] respiratory system, the likelihood is that [child] will work harder than a child without [name of condition] and will need extra support.*
>
> *PID B*

This will depend on the child's comorbidity, and other parents described their child being able to 'fight' infections like a child with no comorbidity,

> *[child] has never ever had a chest infection (…) So, infections and coughs and colds [child] should be able to fight them like a normal child. And [child] has been doing, (…) last year we had no chest infections and January this year we've just had coughs and cold and now because of [describes condition]. But no, [child] has never, [child's] illnesses, it's never been a problem chest infections until this year. So, it's just I don't know it's just we just take each hour by hour. You know I've just tried to do all the tricks what we was doing in [name of hospital], sitting [child] up and having a humidifier with things going through it and physio, the trained me up in physio there. I could do it anyway but give me a pass certificate. Passed me. I'm just doing all the tricks and try and keep [child] clear as much as possible.*
>
> *PID A*

One parent explained that they fear that their child may suffer from extreme consequences of an infection. It is possible that repeated experiences, or experiences of other children with the same comorbidity, may reinforce this fear in future infections.

> *When [name] gets unwell there's sort of an added and added level and having and having known lots of children with [name of comorbidity condition] who have been intubated multiple times in the first few years few years of their life that was obviously my brain kind of immediately went, oh God [child's] going to end up incredibly unwell and intubated and that you know unfortunately is what happened.*
>
> *PID B*

Antibiotic use for BATCH trial illness episode

The child's comorbidity may impact on antibiotic use in different ways. The child's vulnerability due to their comorbidity may have an impact. For PID A, the child had a life-limiting condition, and was vulnerable to infection, and the child's chest infection needed to be treated in addition to treatment for an additional physical injury.

> *Everything what was going in was needed, I mean [child] was that bad they put [child] on drugs almost like straight away because [child] actual operation was halted and it was done awake her operation by the way*
>
> *PID A*

> *[child] was given the epidural because [child] chest infection it was either get it done because it needed to be done this (you know or they were more worried about the chest infection that [child] wouldn't wake up. Said outright you know what I mean but it had to be done. They give [child] a good few days of antibiotics going through, you know through [child's] arm and that before we did it. I didn't even think they mentioned disadvantages [of antibiotics] I didn't hear him 'cos I just see them as an advantage, get them in and sort [child] out.*
>
> *PID A*

The implications associated with a child's comorbidity may also result in other non-antibiotic management options being eliminated or seeming to be less appealing. For PID C, the child had a blood condition which meant that their blood does not clot properly, and therefore an operation had particular risks associated with it. The parent felt that in a choice between an operation and antibiotics, antibiotics were the preferred management route,

> *I said can we not just do the antibiotic route to avoid an operation all together and that's what they decided to do. So yes, so that's what we went with, we went with the antibiotics route.*
>
> *PID C*

This may differ between children and conditions. Patient PID B was started on antibiotics as a 'precaution' but stopped as their infection was found to be viral.

> *I think actually they might have put [child] on something just in case while they did their viral panels just so that if there was anything that needed antibiotics they could have already started treating it. [Child] then came off those antibiotics because there was nothing that needed treating and then [child] caught pseudomonas as well we were there so they put [child] back on a very aggressive course of antibiotics for about 4 days I think.*
>
> *PID B*

However, a sputum sample then showed a secondary bacterial infection and they were started on antibiotics again. At this point, the infection required aggressive antibiotic treatment

> *It needs a very very aggressive form of antibiotics as well because there are quite a lot of antibiotics that it just doesn't respond to. So I mean the one that they put [child] on when [child] was in the consultant described it to me as basically a Dettol that kills 99.9% of most bacterias and I was like well as long as it gets rid of the (18.39) that's the main thing really. But yes it was an aggressive infection it was treated aggressively but I'm just hoping that it doesn't kind of rear its head too much in the future.*
>
> *PID B*

Use of IV antibiotics

To some parents, IV antibiotics are perceived to be quicker and more effective.

> *Well first [child] was intubated so orally wouldn't have worked for [child] anyway obviously [child's] got a nasogastric tube so it could have gone down there. But I mean [child] has you know direct access at all times that we were in so I think the impression was that get it in quicker and its more effective if you were goes straight into the blood stream so that was the impression that I got in they wanted to treat it quite aggressively because pseudomonas are especially you know one of those things that are quite resistant to many antibiotics.*
>
> *PID B*

> *[Child] stayed the end stage using it on an IV basis yes.*
>
> *PID B*

> *yes and [child] you know [child] wouldn't traditionally [child] wouldn't (you know I've said that traditionally child's) orally anyway because [child] doesn't have anything orally. But down [child's] NG I think you know whilst [child] has access in it just sort of made sense to pop it in via that whilst we had other things going through there anyway.*
>
> *PID B*

However, this will differ between types of comorbidity. For example, other children may take antibiotics orally as well.

> *So they were given intravenously until I think it was Sunday evening so [child] had [child's] last, so they were, [child] was given two different antibiotics and one can only be given intravenously and [child] had [child's] last on Sunday and the other one can be given orally and intravenously but they gave it to [child] intravenously until the other one finished so now [child's] still on the one that you can have both ways. So [child's] having that one merrily now.*
>
> *PID C*

> *the drip was going on while [child] was having them orally as well yeah for an extra couple of days.*
>
> *PID A*

Decision to switch and/or stop antibiotics

Two parents mentioned being anxious or surprised when the antibiotics were switched or stopped.

PID C felt that they could have had more warning, implying perhaps that there could have been further communication around the decision. However, they implied a notion of 'trust' in HCPs and their decisions.

> *I was a little bit anxious in the fact that I thought maybe you know it might be happening too soon. But then again you [child's] behaviour and [child] just looks a lot better and so you know you've just got to trust what they're doing. I mean [child] did have a bit of runny stomach when [child] moved over I think it is still a bit runny or upset tummy when [child] moved over to the oral antibiotics which we weren't expecting and they said to us it's from having oral antibiotics. It would have been nice to have a bit of a warning to say that you know you can expect this but yes.*
>
> *PID C*

PID B was informed after the antibiotics had already been stopped for their child. While they implied some surprise as the consultant had implied their child would be on antibiotics for longer, they reported that their child had been fine since stopping.

> *I came in one day and they said [child's] infection markers are low enough that [child] doesn't need to be on antibiotics so we've stopped them.*
>
> *PID B*

> *I was a little surprised because the consultant had said [child] would be on them for 7 to 10 days at least and then it was sort of day 4 they said oh actually*
>
> *PID B*

> *[child] doesn't need to be on them so we've taken [child] off them [child's] been fine since yes.*
>
> *PID B*

However, one parent appeared to imply that there were regular discussions around antibiotic treatment and decisions for their child.

> *They had all them discussions every day like I said they should have stopped the intravenous but they wanted to carry on for two days just to make sure and then coming home they just had like an extra four or five days just to take that precaution, even though [child] would have been off it just an extra couple of days.*
>
> *PID A*

Duration of antibiotics

Parents' views on the duration of the antibiotic course may differ according to the child's circumstances. One parent felt that, with monitoring, the antibiotic duration for their child could potentially have been shortened.

> *I think overall I think it was a good stretch of time in terms of shortening it I think maybe [child] didn't quite need to be on the antibiotics for as long as [child], for another 5 days if that makes sense? I can understand (19.23) but maybe if [child] was a bit more closely monitored [child] might not need to be on it for such a long time.*
>
> *PID C*

However, another parent whose child has a life-limiting illness described their parental desire to protect their child and would not have wanted antibiotic treatment to be shorter. As PID A explains

> *definitely not shortened if it was left to me, as the mum that I am, I would have [child] on it all the time to keep the bugs away you know, obviously you can't but for safety reasons and the way (21.47) antibiotics for the rest of [child's] life [child] could be here longer, so I think like that.*
>
> *PID A*

Comorbidity and antibiotic resistance

Some parents of children with comorbidities may be aware of the consequences of the unnecessary overuse of antibiotics. Parent PID B demonstrated awareness of the need to balance delaying antibiotics unless certain that they are needed (due to antibiotic resistance), with the serious consequences of delaying antibiotics for their individual child.

> *The whole thing is you know starting [child] on antibiotics when we weren't a 100% sure that [child] needed them was a bit kind of you know is this really necessary. But actually, I think especially with [child] it it's kind of its necessary to be slightly more cautious so you know it's like you say it's a tricky line to tread really isn't it between giving them unnecessarily and also making sure that you're not delayed in giving them and therefore it's more of an issue to solve than in the first place.*
>
> *PID B*

> *You know I'm wary of the fact that there's talk about antibiotics resistance the more you take them the less likely they are to work. But I think with some things you know they are necessary and you know I wouldn't I wouldn't want to just pop him on antibiotics just to treat everything. But I think you know when you've got something that is in the process of being checked the results are going to come in the next day I don't I wouldn't want [child] on for 2 weeks rather than waiting for results. But at the same time you know if it's if it's potentially stopping something growing into something worse then I think it's a good use. But yes, I am I am wary of the fact that if [child] does have pseudomonas which are something that are going to keep coming back then [child] may end up being on antibiotics quite frequently.*
>
> *PID B*

Parents' views on impact of comorbidity on participating in a clinical trial

Concerns about taking part in a trial

One parent (PID B) described that they would not feel any 'extra' concern about their child taking part due to their child's comorbidity.

> *I think it would be it would be a distress level thing because the same would go for my [other child who does not have the comorbidity] but I wouldn't put [child] anything additional to create a part you know to be a part of something.*
>
> *PID B*

Parents did not appear to express significant additional concerns about taking part in a clinical trial due to comorbidities. One felt that it did not make any difference to their child's treatment (PID A), and one could not understand why people would not want to take part in it because it is not invasive (PID C). For some, their main concerns were the same as parents of children without comorbidity (see *Chapter 5*), whether they would be taking extra blood.

However, PID B did describe their child as difficult to get blood from but felt reassured that the trial sample could be taken at the same time as routine bloods.

> *[Child's] very hard to get blood from anyway and [child's] tricky to access so I didn't really want to subject [child] to anything you know over and above what was necessary.*
>
> *PID B*

Parents also felt that the decision would be about minimising the risks for their child but again implied that this would be the same regardless of comorbidity,

> *I think it would need to depend on the risks involved. I think yes if something was you know if they were more risks of procedures being more risky one way or another I'd probably go on the less riskier route if that makes sense I suppose that's for everybody you know.*
>
> *PID C*

Barriers to participating

Parents explained that if a study involved them needing to bring their child to have extra bloods this would be a barrier to them participating.

> *It would just, my main concern would be causing [child] extra distress or harm in any way you know if [child] needed extra bloods doing, or bloods that [child] wasn't already having done you know [child] said do you want do you want [child] to take part in this study you're going to have to bring [child] in every week for bloods then I probably wouldn't.*
>
> *PID B*

Another parent who was interviewed earlier than intended and did not have a second meeting with the research nurse described that they wanted their child to avoid an operation, due to their comorbidity and the possible risks involved, and instead take 'the antibiotic route' which had implications on their decision to participate in the trial if it meant they did not receive antibiotics (PID C).

Facilitators to trial participation

Similarly to parents of children without comorbidities, parents demonstrated altruism in their reasons for participating in the trial and of 'giving back'.

> *When I got looked after and [child] got looked after in there it was, the way they was it was [recording unclear – (?)think] I had no reason not to take part, giving back, you know what I mean it's nice giving back to people who could learn off [child].*
>
> *PID A*

Another parent felt that the research was interesting.

> *I would like to say I'm very appreciative that there are these studies and trials going ahead because they're very interesting and it's nice to part of them so I think I'd quite to just say that you know it's nice to be given the option.*
>
> *PID C*

Another parent described the importance of research in relation to reducing unnecessary use of antibiotics.

> *I think you know whether kids you know they can stop giving them antibiotics unnecessarily and we can if we can discover quite quickly whether they need them or not that's obviously going to benefit them was there talk about whether it would stop the spread of superbugs and things because of not using antibiotics unnecessarily was that part of it as well?*
>
> *PID B*

One parent appeared to feel that the research may benefit their child as learning how to treat children more efficiently is going to benefit their child if they return to hospital again in the future.

> *When they asked about you know being in part of the trial because it wasn't going to make, it wasn't going to inconvenience me or [child] in anyway especially [child] I was happy to take part in it, or for [child] to take part in it purely because you know if it's going to stop the spread of bugs and things and we can treat children more efficiently then that's going to benefit [child] in the future because I know that you know at some point in [child's] in [child's] life [child's] probably going to end up back there that's something that will potentially benefit [child] in the future anyway.*
>
> *PID B*

Finally, one parent described how they would be particularly motivated to participate in a trial relating to their child's specific comorbidity.

> *If it was specific to [child's comorbidity condition] then absolutely, you know there's always a chance that they can you know discover a new way of treating [child's comorbidity condition] and all the rest of it and if it's something that's going to benefit [child] or other children in long time like bacterial studies and things, yes absolutely I would.*
>
> *PID B*

Healthcare professional views on impact of comorbidity on management

This section specifically reports on HCP views relating to the influence of comorbidities on management decisions. More general findings from the SWAP data (e.g. general advantages and disadvantages of PCT and algorithm, barriers and facilitators to implementation, and reflections on the trial processes) which do not relate specifically to comorbidities will be integrated with the main trial results.

Influence of comorbidity on management

Value of PCT test Some HCPs talked about finding the PCT test less useful for certain patient groups. One HCP explained that they were not finding the test useful for surgical abdominal patients (PID05). Another felt that while it gives a strong indication of bacterial infection, they still did not know how reliable the PCT is in different sorts of infections, for example, mycobacterial or parasitic infections, and how to interpret results in light of that. Uncertainty over which groups the PCT test may be useful for may then impact HCPs' perceptions, the reliability and value of the test.

> *I guess the problem is understanding the different types of infections and how reliable the PCT is in different sorts of infections, for example, things like mycobacterial infections how reliable are they or in parasitic infections for example I guess there's still question marks, I'm not sure are well answered in the literature and how do we interpret these, that's one of the draw backs of it, it just gives us a kind of strong indication of a bacterial septic kind of child, for example.*
>
> *PID35*

> *I know that we don't recruited children with complicated bone infections, maybe barriers would be if you can't use it for all conditions it can be used in certain things then people would just rather use one. They would rather see one blood test.*
>
> *PID32*

However, some HCPs also talked positively about the intervention, particularly with certain patient groups, including medical patients rather than surgical patients (PID5), epilepsy, neurodevelopmental delay, neurological, and cardia (PID29), oncology (PID35) and conditions where there is a real uncertainty about the cause of the deterioration.

> *Children with comorbidities such as epilepsy or neuro developmental delay or things like that I actually think it's even more helpful in these group of children. Because often there's a real uncertainty about what is the cause of deterioration, you know is it a chemical pneumonitis due to aspiration, is it a general decline in their you know in their in their condition. So, in that respect being able to rule out infections early on and stop antibiotic early would be even more helpful.*
>
> *PID29*

> *In a child that has very poor lungs very you know very bad heart very you know they might be seen for reasons. I will imagine that if I will find even more useful in children with comorbidities than in healthy kids.*
>
> *PID31*

> *Complicated situations are when we do not know or are suspecting that this is something else like oncological or inflammatory, I think that procalcitonin would have a significant value in those type of patients that are diagnostically challenging.*
>
> *PID35*

The PCT test was seen by some HCPs as an additional piece of information that would be useful for complex patients who might be more likely to get more unwell.

One HCP, PID31, felt that the PCT test and algorithm might be particularly useful with neonates and may potentially be able to help reduce antibiotic use,

> *in paediatrics in groups that routinely will get antibiotics like neonates, but you know very easily they will get into the emergency department and all of them get a screen all of them get you know, I think in those groups a procalcitonin will also be very useful.*
>
> *PID31*

Some HCPs talked about having a lower threshold to prescribing antibiotics or more caution over certain children with comorbidities.

One HCP, PID33, talked about a tendency to a slightly longer duration of antibiotics for chronic patients,

> *probably yes if that group of patients probably does make you more cautious about making sure that they a decent course has been given and I can't remember changing our interpretation for PCT results in any way. I think yes there are occasions in that cohort where you think where you think that a slightly longer course of antibiotics would probably be necessary to make sure that we've definitely treated that, the chest in this scenario. But like I say I just can't I can't recall relating to the study itself whether we changed decision making because of the procalcitonin there may be a bit of a tendency towards giving a slightly longer course in some of those chronic patients just from a purely clinical point of view.*
>
> *PID33*

Similarly, HCP PID32 appeared to suggest that there might be a tendency for HCPs to have a lower threshold to treating patients with comorbidities with antibiotics,

> *I feel that sometimes when they make decisions about antibiotics the children with comorbidities they probably treat them longer and have a lower threshold to treating because of the comorbidity. So they want to stop them getting sicker quicker and more harshly than maybe they would for just a child without comorbidities.*
>
> *PID 32*

Another HCP, PID35, appeared to try to resist 'generalising' about certain comorbidities, but nevertheless implied that certain patient groups would have more antibiotics,

> *don't want to generalise too much by saying certain conditions, for example, you know children with significant cerebral palsy with really terrible chest infections and recurrent chest infections and known to have recurrent chest infections they might experience a lower threshold of stopping antibiotics and having more antibiotics because of a bowel infection for example, yeah I guess there are certain clinical groups that would have more antibiotics.*
>
> *PID35*

Use of algorithm

Some HCPs (e.g. PID31, PID33 and PID35) felt that comorbidities would not necessarily make a difference in whether they were more or less likely to adhere to the algorithm.

> *I probably will use more in children with comorbidities but I don't think they interpretation will be, or how will I act. It will depend on the level severity than on the comorbidities if that makes sense.*
>
> *PID31*

However, one HCP, PID32, surmised that doctors generally might be less likely to adhere to the algorithm for children with comorbidities, for example, cardiac babies, children with cerebral palsy.

> *I feel like it's hard to say because I don't I can't really think of like sort of groups of kid with comorbidities that we particularly see other than our cardiac babies and I think the doctors would use it less in the cardiac babies. Like they wouldn't adhere to the PCT algorithm as much as they would for sort of typical child having their appendix out and I think it comes back to they're more worried and more cautious with those children and maybe that's the same for the children sort of with cerebral palsy, child that come in with chest infections they're probably less likely to use the PCT because they want to make sure the child's clear.*
>
> *PID32*

Another HCP, PID33, explained that it may be more 'tricky' to interpret improvement clinically for a patient with comorbidities, and that the PCT result and its interpretation may help in these situations.

> *I can't recall treating them any differently I think in interpreting the result only that there there sometimes being a more tricky interpretation of the clinical picture in some of those patients as to whether they're improving or not improving. I think with some of the sort of respiratory failure of chronic patients its sometimes difficult to appreciate an improvement in a chest x-ray picture, or not, that often probably led us towards continuing, I can't think of any particular different interpretation of the PCT result that we made in that context. I think it may well have facilitated things a little bit better because you felt that there was less to go on clinically.*
>
> *PID33*

This could then be used to potentially stop antibiotics sooner,

> *if it was reassurance that things were improving biochemically that probably would have factored in to being able to stop a bit sooner. Yes, I can only see it as a benefit more than a hindrance in these particular cases.*
>
> *PID33*

Implementation of intervention

Barriers to implementation

Many of the barriers to implementation of the intervention were general and align with those found in the main trial (see *Chapter 5*). However, potential barriers to using the intervention relating specifically to comorbidity were:

1. Challenging protocolised behaviour where antibiotic duration is typically set for patients with a specific condition. For example, respiratory patients would be given antibiotics for 2 weeks, or patients with cystic fibrosis where there is a rational for longer duration of antibiotics.

A child with comorbidities may be a repeat user and there may be reluctance from HCPs to use PCT if a negative outcome has been experienced using PCT in the past.

> *I guess if the experience wasn't a good one then these patients will become more challenging because they're more likely to be repeat users and so you know if there would have been an occasion their own personal experience were procalcitonin was gave the wrong advice or the wrong guide then they might be more reluctant to follow the strain subsequent times.*
>
> *PID29*

2. Challenging 'expected' management plan which has been experienced in the past by parents and doctors, for patients who are repeated users, 'I think because like we were just saying about the parents and the doctors of these children they kind of have an idea of what they're going to do anyway and a plan. So, I think that would be tricky' (PID32).

One HCP, PID35, could not see any specific barriers relating to children with comorbidities, unless they were particularly difficult to draw blood from,

> *I guess it's all just blood draw at the moment isn't it there isn't like a point of care test like by the bedside or I don't think it would be a big problem unless you know they're really difficult to get blood from for example.*
>
> *PID35*

There may be a challenge to change 'set' periods of treatment that they might be used to,

> *see as I say the problem with like respiratory patients and stuff they just have a set time they just have a you're getting a week of antibiotics, you're getting 2 weeks of antibiotics, I don't know if a PCT would encourage them to not give antibiotics for the usual what they're what they're expecting to give it for. I don't know if they would get onboard with the PCT.*
>
> *PID5, I2*

3. Another challenge may occur if a child has been looked after before, with repeated attendances, and the HCP knows what works for him – there is an idea of sticking to a particular management plan that works for a particular child, for example, PID32.

> *I also think if they've looked after that child before so, I do the (PICU) studies and we get a lot of children in sort of long term and its same child every winter they'll come in and I think they will look at the child and think well they're normal path of illness is this this and this and we so this this and this, then I think they wouldn't want to use PCT because they already know what they're going to do.*
>
> *PID32*

Related to this, again PID05I2 explains that patients with comorbidities may be inpatients for a long time if they have a line in and get line sepsis or a line infection, they know that they are 'going to get 36 hours worth of antibiotics until the blood cultures are back', or if hospital-acquired chest infection 'we know automatically they're going to get 5 days' of

antibiotics. 'You kind of already know what's going to happen with them', 'but its whether it's worth doing the PCT and they might only end up getting 48 hours instead of the full 5 days and stuff like that you see'.

Facilitators to implementation of PCT intervention in future with children with comorbidity

Many of the facilitators to implementation were general and align with those found in the main trial (see *Chapter 5*). Facilitators or potential facilitators included positive experiences which could potentially encourage more use of PCT.

One HCP, PID32, felt that parents of children with comorbidities may be more knowledgeable about infection markers and the issue of antibiotic resistance,

> *I think maybe a facilitator would be that parents of children with comorbidities often are a lot more knowledgeable about sort of medical things and we often say to them we're currently using CRP and they'll say oh yes we know like the CRP was this yesterday. So, I think they might be a bit more onboard, they'd have a bit more understanding maybe of what an infection marker is and what the importance of antibiotics are, that kind of thing and might be a bit more clued up about antibiotic resistance which they would obviously want to prevent. That's the benefit to them kind of children with comorbidities parents being more willing to accept it.*
>
> *PID32*

Another HCP, PID33, implied that to facilitate roll-out of the intervention would be to discuss the particular value of the PCT and algorithm with parents of children with comorbidities,

> *I wonder whether as part of a sort of parental discussion to say that another piece of information being available to monitor the response to infection and helping to decide when antibiotics can safely be stopped is actually a useful piece of information. Perhaps more so in these patients than others.*
>
> *PID33*

Influence of perceived parental expectations for antibiotics on HCP decision-making

Focusing specifically on issues particular to parents of children with comorbidities, some HCPS felt that parents of children with comorbidities may be more familiar with management of their child and have expectations for a particular management decision.

> *One HCP, PID29, felt 'parents will be a lot more used to using the health services and they will have set expectations of how things are managed'.*
>
> *PID29*

One HCP (PID33) felt that this could particularly relate to expectations around antibiotic use from parents.

> *I think there's a lot of children with chronic illnesses that do have yes higher parental expectations from professional management of those cases. So, they do they do often feel quite involved in the duration of antibiotics', 'there is a certain cohort of patients where the parents are quite actively advocating for courses of antibiotics. So yes, that can sometimes factor into the discussion about whether it's appropriate or not.*
>
> *PID33*

Another HCP, PID32, felt that this could relate to expectations around antibiotic use from both parents and HCPs, if a child has had it before.

> *'The doctors will say oh this is what they always have. The parents will come in and they'll expect them to have the 5 days of (recording unclear) (19.56) and the you know week of tests and that's sort of standard and I think because a lot of these especially the respiratory children are on antibiotics at home so they kind of already have an escalation plan that they stop the antibiotics from home and they come in and they have their IVs. They have that course and then they change back to their normal ones and they go home. But yes, I think it does it definitely has an impact', 'it might be different for the kids that sort of like go in the neurological group where they are less likely to be on antibiotics at home and probably less likely to come in with the sort of chesty side of things'.*
>
> *PID32*

However, on the other hand, this same HCP (PID32) felt that parents of regular attenders may also be more 'clued up' on antibiotic resistance and understanding of infection markers.

> *So, I think they might be a bit more onboard, they'd have a bit more understanding maybe of what an infection marker is and what the importance of antibiotics are, that kind of thing and might be a bit more clued up about antibiotic resistance which they would obviously want to prevent. That's the benefit to them kind of children with comorbidities parents being more willing to accept it.*
>
> *PID32*

Similarly, another HCP, PID31, explained that parents of children with comorbidities may be more familiar with different types of antibiotics,

> *So most of you know most of the parents that have contacts with healthcare setting might have more even medical education. If it is not formal but they might have you know it's not it's not like a healthy child that the parents are very overwhelmed because they've never been in a hospital. These parents are regularly in hospital so they will have learnt the names of antibiotics. So, they have a different relationship with antibiotics but that's nothing to do with the procalcitonin.*
>
> *PID31*

PID05 felt that parents of children with respiratory comorbidities rather than children with other comorbidities were more likely to have expectations about antibiotics,

> *I don't think not when it comes to them, comorbidities. The respiratory ones and stuff yes because if they've been getting, been seen by the respiratory team for so long those parents kind of automatically expect their child to get antibiotics, there isn't kind of any give with those patients because the parents you know it's kind of how they're expected to be treated. But as soon as they know their child's got a chest infection they expect their child to get antibiotics you see.*
>
> *PID05I2*

Healthcare professional views on impact of child's comorbidity on inclusion in a clinical trial

With regards to including children with comorbidities into the trial, one HCP (PID29) felt that at the start of the trial they would not necessarily recruit children into the trial. However, as time went on, they began to include children with long-term conditions. Another HCP (PID5) felt that at the start of their involvement they would leave the decision of whether to involve in the trial to the research nurse, but now they would pass them on more,

> *Probably at the start it did, but probably not now I probably I probably would pass them on more now then leave it up to a research nurse.*
>
> *PID5I2*

In terms of including children with comorbidities in the research, one HCP felt that parents of children with comorbidities may be 'medicalised' and more familiar with research,

> *The ones with comorbidities I think like I said earlier I'm sure because a lot of them are quite medicalised anyway they probably have been in research before or know about research, we get a lot where we go and they say oh yes he's been in everything, so happy to help, because they just want to help. So, I don't think we find patients with comorbidities too challenging.*
>
> *PID32*

One HCP (PID30) when asked whether it was more challenging to approach parents of children with comorbidities to take part in the trial explained

> *No not at all I would say the opposite actually, we had one person who was her little one had really complex, you know not really complex, yes certainly complex needs, and she was absolutely for, her mum said oh yes, you know let me sign up straight away, and some people like you know you were trying to get all the information and then people were like just rushing, yes I'll take part I'll take part you're like no you really do need to understand.*
>
> *PID30*

Discussing PCT test/algorithm with parents

Some HCPs, PID31 and PID33, did not feel that talking to a parent of a child with comorbidities would make a difference in how they talked to the parents about the PCT test. PID31 implies they would not talk about PCT test differently depending on whether comorbidities or not, as not routinely used for either children so would still have to explain. However, PID32 felt that conversations about the test would be different for parents of children with comorbidities in terms of the language that is used and the questions parents might ask.

> *You can definitely see a difference in the language they use, I think it's sort of initiated by the parents. So I could imagine the parent asking like what is the CRP or what is this and then the doctors explain it rather than maybe the doctors going to them and saying the CRP is this and this is the antibiotic and this is what, I think it maybe it would be more initiated but the parent, I definitely think that it would be a different conversation to maybe a child without comorbidities.*
>
> *PID32*

One HCP explained that they did not often discuss the PCT results/algorithm with parents, but when asked they did feel that the experiences of parents of children with comorbidities may make a difference, as

> *every conversation has to be personalised and draw on the patients you know clinical course.*
>
> *PID29*

Discussing the PCT algorithm with parents may depend on which team the child is under,

> *we are not the primary team so we wouldn't necessarily go into these sorts of details unless it was a big deciding factor on the decision that we made using the evidence of the PCT. Then we wouldn't necessarily go into the sort of you know for every patient that would have a PCT that we would happen to be involved with, so no very rarely did that happen.*
>
> *PID35*

Strengths and limitations of qualitative study

The number of parents of children with comorbidities we interviewed was small and the number of parents in the intervention arm is smaller. One parent was also accidentally interviewed earlier than intended. We encountered challenges in recruiting parents due to the heavy workload of sites and other possible factors include burden on patients and staff, exacerbated by COVID-19. However, we believe that by building on the interviews already carried out as part of the main trial, this SWAP has allowed us to gain a deeper understanding of the issues faced by parents of children with comorbidities and HCPs in managing suspected or confirmed infections and comorbidities to tailor future implementation of the PCT if needed.

Triangulation

Triangulation method

Quantitative and qualitative data were analysed separately and written up independently. A triangulation protocol technique was then drawn upon to compare findings. We carried out both data triangulation (using text and numbers) and investigator triangulation (using multiple analysts with different qualitative and quantitative backgrounds).

A shared document was created in which one researcher (JH) summarised the results of both the qualitative and quantitative findings and drafted a triangulation matrix, including a series of statements relating to both the qualitative and quantitative findings, for discussion. Both qualitative (LB-H, JH) and quantitative [Philip Pallmann (PP) and Simon Schoenbuchner (SS)] researchers accessed the matrix online to make comments and provide written feedback.

Following this, a reflective and interactive discussion was held remotely via Teams between quantitative (PP) and qualitative (LB-H, JH) researchers in January 2024 to discuss and revise the summary findings, refine the triangulation matrix and carry out convergence coding. We took each statement in turn to assess quantitative and qualitative findings

and code where there was agreement (convergence), partial agreement (complementarity), dissonance (conflicting findings), or silence (only one data source contributing) (Tonkin-Crine *et al.*[67] and Henley *et al.*, Cardiff University, 2025) An assessment of this was noted in the final column of the matrix.

The summary of results, triangulation matrix and discussion are described in the following sections.

Quantitative results summary

- No evidence of differences between comorbidity subgroups (no comorbidity, single comorbidity, multiple comorbidities) in the treatment effect on IV antibiotic duration or safety.
- Comorbidity category is significantly associated with both clinician behaviour (whether PCT results are considered and whether the algorithm is adhered to) and trial conduct (whether PCT results are available for clinical review), with PCT results *more likely* to be available for clinical review for patients with more comorbidities, and clinicians *more likely* to consider the test result where it is available and follow the recommendation of the algorithm.

Qualitative results summary

Antibiotic use in trial illness episode

- Comorbidity appears to influence perceptions of antibiotic use, with considerations for the child's vulnerability and the necessity of additional treatment.
- Parents of children with comorbidities can assess what is 'well' for their child personally and may have an ongoing relationship with healthcare workers.
- Some parents of children with comorbidities may have expectations for antibiotic use but may also be aware of the issue of antibiotic resistance.
- The perception of antibiotic duration may differ for children with life-limiting conditions.
- Some parents may trust healthcare providers' decisions but may desire more information regarding changes in antibiotic treatment.

Procalcitonin efficacy and algorithm

- Some HCPs expressed reservations about the utility of the PCT test for certain patient groups, such as patients with surgical abdominal infections. Uncertainty existed about the reliability of the PCT test in different types of infections, which may impact on HCPs' confidence in its value. However, despite concerns, HCPs also highlighted positive aspects of the intervention, especially for complex patients with comorbidities, where the PCT test provided additional information.
- Views on adherence to the algorithm varied among HCPs. While some believed comorbidities might not significantly affect adherence, others suggested doctors might be less likely to adhere to the algorithm for certain groups, like patients with cardiac conditions or cerebral palsy.
- Challenges in interpreting clinical improvement in patients with comorbidities were acknowledged, and the PCT result was seen as potentially aiding in such situations.

Triangulation results

Four statements were produced (see *Table 44*). There was partial agreement between quantitative and qualitative data sources for the first two statements, dissonance for the third and silence for the fourth.

There was partial agreement for statement 1, comorbidity status impacts the perception of the reliability of PCT. Quantitative findings show that HCPs were significantly more likely to take the PCT test into consideration with

TABLE 44 Study within a project triangulation matrix

	Statement	Qualitative findings	Quantitative findings	Convergence coding
1	Comorbidity status impacts the perception of the reliability of PCT	*Partially agree* Some HCPs find PCT test less useful for specific patient groups, for example, surgical abdominal infections; some suggested that for other patient groups (e.g. oncology, epilepsy, neurodevelopmental delay) PCT test could be more helpful	*Agree* PCT tests were significantly more likely to be available for clinical review, and clinicians were significantly more likely to take the PCT test into consideration, with increasing number of comorbidities	Partial agreement
2	Comorbidity status impacts adherence to the PCT algorithm	*Partially agree* Views on adherence to algorithm varied among HCPs. Some believed comorbidities might not significantly affect adherence, others suggested doctors might be less likely to adhere to algorithm for certain groups, for example, cardiac or cerebral palsy patients	*Agree* Clinicians were significantly more likely to adhere to the PCT algorithm with increasing number of comorbidities	Partial agreement
3	Comorbidity status impacts duration of antibiotic prescribing	*Agree* Expectation of antibiotic duration may differ for children with comorbidities, with some parents preferring longer courses for safety, especially for children with life-limiting conditions	*Disagree* No significant difference in antibiotic duration or safety was found across comorbidity subgroups	Dissonance
4	Comorbidity status impacts expectations for antibiotic prescribing	*Agree* Both HCPs and parents may have expectations that children with certain comorbidities have antibiotics as routine. However, while certain comorbidities may increase expectations around antibiotic use, some parents might also be knowledgeable about antibiotic resistance, because of regular contact with clinicians	No data	Silence

increasing *number* of comorbidities, whereas qualitative findings show that the *type* of comorbidity may make a difference to HCPs' perceptions of how useful the PCT test is. Here, the data collected provide information relevant to the statement in slightly different ways but both show that comorbidity does appear to have an *influence* on perceptions of the reliability of the PCT test.

There was also partial agreement for statement 2. However, while there is partial agreement that comorbidity status *impacts* adherence to the PCT algorithm, the impact may not be in the same direction. Quantitative findings show that HCPs were significantly more likely to adhere to the PCT algorithm with increasing number of comorbidities. However, qualitative findings suggest that HCPs may be less likely to adhere to the algorithm for certain patient groups, for example, those with cerebral palsy.

There was dissonance for statement 3, comorbidity status impacts duration of antibiotic prescribing. While qualitative findings suggest that there might be an expectation for some children with comorbidities to receive longer courses of antibiotics, given the quantitative data available we were not able to find evidence of differences between comorbidity subgroups in the treatment effect on IV antibiotic duration. This may be due to the fact that the quantitative study was not a priori powered to detect such an effect.

There was silence for the fourth and final statement, comorbidity status impacts expectations for antibiotic prescribing. The quantitative study did not investigate the expectations of parents and HCPs for antibiotics, so we coded this as silence as there was only data available from the qualitative source. Qualitative findings suggest that both HCPs and parents may have expectations that children with certain comorbidities (e.g. respiratory conditions) have antibiotics. However, possibly because of regular contact with clinicians, parents might be knowledgeable about antibiotic resistance.

Limitations of the study within a project triangulation

As described above, the sample size for the qualitative study was very small, particularly for parents. Therefore, it is helpful, to consider the results in relation to the quantitative findings in this triangulation process. The qualitative study can uncover individual cases and provide a narrative around those cases which are different to the 'norm' or the average. The quantitative study can provide an overall summary of the 'bigger picture' of management of a much larger sample of patients.

It is worth noting that the quantitative study did not separate out comorbidities by severity, but only counted number of comorbidities. Therefore, the effect of severity cannot be included in the triangulation process from the quantitative data source.

Finally, not finding 'full agreement' between quantitative and qualitative data sources on any of our four statements could be attributed to investigators exploring different aspects of the trial experience within the two studies. It is possible that by planning a more integrated triangulation process earlier in the study design we could have ensured that the data we collected complemented each other more fully. However, we believe that the triangulation process we have carried out, including both data (number and text) and investigator (quantitative and qualitative researcher perspectives) triangulation, still provides us with a more rounded picture of the BATCH SWAP findings.

Chapter 7 Discussion

Summary of results

This trial provides seminal evidence in an area where there is a paucity of robust data to inform optimal duration of IV therapy for bacterial infections in children. Such robust data have never been more essential than now, with increasing AMR posing a 'catastrophic threat', as described by the previous Chief Medical Officer, Dame Sally Davies.[68] AMS, which includes prescribing shorter antibiotic courses, is a key component of the armamentarium against the global crisis of AMR. The trial results fill a significant evidence gap highlighted by a systematic review and meta-analysis[16] and two NICE research recommendations.[7,11]

Quantitative study

We demonstrated that there was no evidence of a treatment effect on any primary or secondary outcome, either overall or in any subgroup. The estimated treatment effect for the composite safety outcome was consistent with non-inferiority. We therefore conclude that making the results of the PCT-guided algorithm available to clinicians was non-inferior with respect to safety and did not result in reduced antibiotic duration in hospitalised children with suspected or confirmed bacterial infection.

In considering the trial design, we were concerned about contamination, so we devised strategies to retain control of the PCT test within sites, which worked – no patients in the UC group had a PCT test. However, this also meant that the process of getting a PCT test and result was not embedded into routine practice. On reflection, a cluster RCT design might have been more appropriate.

Health economics study

The PCT test in itself is not very expensive (£14); nevertheless, it does contribute to a modest reduction in the number of hours of IV antibiotic administration. Results of the cost analysis of complete cases were also higher in the PCT arm for all age groups and for children aged 5 and over. The intervention is not cost-effective as it is more expensive with no significant improvement in IV antibiotic duration, even though it resulted in a non-significant improvement in HRQoL. Productivity losses are similar in both arms. It should be noted that income losses of around £200 during a child hospital stay are significant for families.

Qualitative study (main trial)

Healthcare professionals overwhelmingly described the PCT blood test as fitting in with their usual practice of taking bloods for monitoring clinical response. The time taken to get the PCT result was an important issue brought up by HCPs, with variable accounts and experiences in terms of the time taken to get the result. In some sites, the turnaround for test results was quite slow, but in others it was available 'within a few hours'. Some HCPs described not receiving the test result in time for the ward round, therefore meaning that a decision about antibiotics may have been made before the HCP had seen the PCT result. On such occasions, it appeared that the algorithm could not therefore be consulted.

Some HCPs talked about PCT being useful to support antibiotic discontinuation or de-escalation decisions, and one HCP talked of PCT as an 'extra weapon' to convince prescribers to stop antibiotics, especially if the CRP was borderline. However, related to this is the feeling from some HCPs that this must be balanced against the high risks of deterioration in this very sick cohort of children. Some HCPs described their local setting as having robust AMS programmes, with microbiology and ID team ward rounds, and in these settings the 'added' value of the intervention was perceived to be

less. Use of the algorithm appeared to be more challenging when the PCT test gave a result that was inconsistent with the clinical picture: High PCT level in a clinically well child and low PCT level in a clinically unwell child. In situations where the algorithm and clinical judgement did not align, some clinicians described anxiety or nervousness over what to do, whereas others stated quite clearly that they would follow their clinical judgement. Some HCPs recalled that the algorithm was open to be variably interpreted by those who may follow the spirit of it but not the exact letter of it, as the trial itself was a pragmatic trial. However, despite the pragmatic nature of the trial, some HCPs more openly expressed cynicism about following algorithms and protocols.

Acceptability of the intervention from the perspective of parents focused on two main themes: concern over extra blood taken, and deviation from usual practice. Overwhelmingly, parents described their initial concern over the potential need for extra blood to be taken for the purposes of the trial and for the PCT test. They felt that their child had been through enough and wished to minimise the trauma of extra blood. Some parents expressed concern that taking part in the trial and/or receiving the intervention might mean deviation from the usual management their child would receive, which could result in a longer recovery time, a longer duration in hospital, or a lengthy delay while waiting for test results. However, generally they did not feel that the trial had had a negative impact on their child's management, and described feeling reassured that the HCP's clinical judgement was still the overriding factor in their child's treatment decision.

Qualitative study (study within a project substudy)

Parents felt that the child's comorbidity and their need to deal with ongoing health challenges may impact on the child's illness 'tolerance' allowing parents to gauge when there is something 'seriously wrong'. Their child's comorbidity meant that they felt they had to be more careful if they get coughs and colds due to their lower immune system, meaning they believed they needed more 'support' to fight an infection, including IV antibiotics. Two parents mentioned being anxious or surprised when the antibiotics were switched or stopped, and felt that they could have had more warning, implying perhaps that there could have been further communication around the decision. However, they implied a notion of 'trust' in HCPs and their decisions. Parents' views on the duration of the antibiotic course differed according to the child's circumstances; one parent felt that, with monitoring, the antibiotic duration for their child could potentially have been shortened, but another parent, whose child had a life-limiting condition, described their parental desire to protect their child, and would not have wanted antibiotic treatment to be shorter. Parents did not appear to express significant additional concerns about taking part in a clinical trial due to comorbidity but felt that if a study involved them needing to bring their child to have extra bloods this would be a barrier to them participating. Similar to parents of children without comorbidities, parents demonstrated altruism in their reasons for participating in the trial and of 'giving back'.

Some HCPs talked positively about the trial intervention, particularly with certain patient groups, including medical patients rather than surgical patients, neurological, cardiac and oncology conditions where there is a real uncertainty about the cause of the deterioration. There was a tendency to a use slightly longer duration of antibiotics for patients with comorbidities, and to have a lower threshold to treating patients with comorbidity with antibiotics. Some HCPs felt that comorbidities would not necessarily make a difference in whether they were more or less likely to adhere to the algorithm.

Many of the barriers to implementation of the intervention were general and align with those found in the main trial. Potential barriers to using the intervention relating specifically to comorbidity were: (1) challenging protocolised behaviour where antibiotic duration is typically predefined for patients with a specific condition (e.g. respiratory patients are typically given IV antibiotics for 2 weeks), (2) children with repeated attendances requiring IV antibiotics where the HCP knows 'what works for them' and (3) that parents of children with comorbidities may be more familiar with the management of their child and have expectations for a particular management decision which may include a long course of IV antibiotics. With regards to including children with comorbidities into the trial, there may have been initial reluctance at the start of the trial, but as time passed and familiarity with the intervention and the algorithm grew, more children with long-term conditions were included.

Previous research

These findings are inconsistent with those from three previously published studies:

1. The Neonatal PCT Intervention Study (NeoPInS) multicentre RCT, which demonstrated that PCT-guided decision-making was superior to standard care in reducing antibiotic therapy in neonates with suspected early-onset sepsis.[69]
2. The PROcalcitonin to Reduce Antibiotic Treatments in Acutely ill patients (PRORATA) trial of adult patients which demonstrated PCT-guided antibiotic treatment substantially lowered antibiotic exposure and was non-inferior to standard care.[70]
3. The PROcalcitonin to Stop Antibiotics after CArdiovascular surgery in a pediatric intensive care unit (PROSACAB) study which implemented a PCT-guided protocol to stop or de-escalate antibiotic treatment in children after cardiovascular surgery demonstrated that after implementation of the protocol, the rate of antibiotic de-escalation was higher, with an average reduction of 1.1 days of antibiotic treatment, without an increase of adverse outcomes.[20]

A systematic review and meta-analysis of hospitalised adult patients reported that PCT-guided antibiotic therapy was shown to be effective and safe in the reduction of antibiotic duration in both sepsis and respiratory tract infections. There was no statistically significant difference in length of hospitalisation, recurrence of infection, rehospitalisation, and 28-day mortality, but in-hospital mortality was significantly reduced.[71] A recent systematic review and meta-analysis of PCT-guided antibiotic therapy in critically ill adult patients reported that PCT-guided therapy may be associated with reduced antibiotic use and lower 28-day mortality but higher infection recurrence with similar ICU and hospital length of stay.[72]

A propensity score-matched cohort of adult patients with LRTI did not find any effect of a PCT-guided algorithm on duration of antibiotics, which it concluded was due to poor implementation of the algorithm.[18]

There are a number of possible reasons for our findings. First, we used a specific test platform in the design, with restricted access to PCT tests only for the trial, to avoid potential contamination of the control arm by making PCT testing available on routine hospital high-throughput laboratory analysers. Even though the chosen test platform was an assay which was quick and simple to use, the fact that it did not align to the patient pathway meant that results were not always available at clinical reviews. Second, despite the fact that site research teams were trained in use of the PCT algorithm, and there were stickers and credit card-sized laminates for staff lanyards produced for use by the clinical teams, adherence to the PCT algorithm was low (38% at first clinical review, and 57% at any clinical review). Poor adherence to the algorithm may have undermined its effectiveness in reducing duration of IV antibiotics. Third, the four lead sites that contributed the most participants [1611 out of 1949 (83%)], all had dedicated consultant-led paediatric AMS programmes, conducting AMS ward rounds at least three times a week.[73] These four study sites had already implemented most of the evidence-based and consensus-led recommendations for paediatric AMS by the time the trial started recruiting.[74]

Strengths and weaknesses

This trial has several strengths; it was designed to be pragmatic, and therefore represent routine clinical practice in diverse settings, including both district general hospitals in ethnically diverse and deprived areas, and teaching hospitals in cities. We used coprimary outcomes which considered both effectiveness and safety to ensure that participants are not harmed in the promotion of AMS. The cost-effectiveness analysis demonstrated that the intervention was not cost-effective and therefore has limited potential to improve healthcare system value.

Limitations of the trial are that robust AMS programmes were already implemented in the lead recruiting sites and that adherence to the algorithm was poor. Introducing an antibiotic guidance algorithm (protocolisation) was in itself an intervention, because it changed clinician behaviour by raising awareness of antibiotic prescription, and by providing clinicians with a 'formula' which can be applied to other biomarkers like CRP or white cell count to guide antibiotic prescribing. This may have led to increased antibiotic prescribing awareness in both arms of the study. We assessed this

in the pilot study utilising observational and qualitative methods but did not find any evidence to support this. Clinicians and participants were not blinded to the treatment arm, as we believed this approach tested the utility of the protocol, rather than just the utility of PCT on its own. Additionally, blinding would have involved taking a 'dummy blood sample' in the control arm, which would not have been ethically acceptable in children.

Another significant limitation was poor adherence to the algorithm. Some of this was due to unavailability of the results in time to make decisions, or to clinicians not trusting the test result enough to use it to make antibiotic decisions. Possible consequences of low adherence include not only failure to detect effectiveness with respect to antibiotic use but also the risk of falsely claiming non-inferiority with respect to the safety outcome.[57]

Another limitation is the fact that the vast majority of enrolled patients were from tertiary centres even though nine district general hospitals (DGHs) were participating in the trial. This may limit the generalisability of the results, as it may be that a PCT-guided algorithm could be effective in DGH settings (where there are not robust AMS programmes) but not in tertiary centres. Work to improve recruitment from DGHs would be important for future RCTs.

This trial adds to the body of evidence on the effectiveness of PCT-guided algorithms in reducing antibiotic duration in hospitalised children already on IV antibiotics, but it does not address the question of whether PCT use reduces antibiotic initiation in children presenting to the ED. There are two NIHR HTA-funded trials due to report soon, which will provide further evidence: The PROcalcitonin and NEWS2 evaluation for Timely identification of sepsis and Optimal use of antibiotics in the emergency department (PRONTO) trial, which recently completed recruitment of 7676 adult patients with suspected sepsis presenting to the ED, will determine whether a PCT-guided risk assessment can lead to a reduction in IV antibiotic initiation,[75] and the BiomArker-guided Duration of Antibiotic treatment in hospitalised PaTients with suspected Sepsis (ADAPT-Sepsis): the ADAPT-Sepsis trial will evaluate whether a treatment protocol based on monitoring CRP or PCT safely reduces antibiotic duration in hospitalised adults with sepsis.[76]

Future studies of biomarker-guided interventions should utilise adaptive platform trial designs embedded in routine clinical care to comprehensively evaluate multiple diagnostic tests, in order to robustly and rapidly establish clinical utility, safety, cost-effectiveness and implementation outcomes. A sociotechnical understanding of whether, how and why clinicians act on information from diagnostic tests to make antibiotic prescribing decisions will improve trial intervention fidelity and facilitate implementation and adoption of tests shown to be effective and safe. AMS is a multicomponent health service activity, influenced by a range of interdisciplinary, organisational, service-level, professional, individual and behavioural factors,[77] and future trials must build in comprehensive exploration of this hidden complexity to ensure the success of future implementation. Diagnostic stewardship demands that tests are performed at the right point in the clinical pathway, on the right patients, in the right way, with results interpreted correctly, to improve clinical decisions about severe infection.

In hospitalised children treated with IV antibiotics for suspected or confirmed SBI, a PCT-guided algorithm is safe but not effective in reducing IV antibiotic duration, especially where robust AMS programmes are already implemented. Implementation frameworks are required to ensure intervention fidelity in biomarker-guided trials.

Findings of interest

Clinicians may be reluctant to adhere to biomarker-guided algorithms, due to unfamiliarity with interpreting the test result. In the presence of robust AMS programmes to reduce antibiotic use, a PCT-guided algorithm may offer little added value.

Impact and learning

Education and training programmes on AMS and diagnostic stewardship are important components of improving judicious antibiotic use.

Future trials must build in comprehensive implementation frameworks to ensure fidelity of the intervention.

Implications for decision-makers

The BATCH trial was funded based on NICE research recommendations, and based on the results reported in this report, we do not recommend the routine use of PCT to guide antibiotic duration in hospitalised children with suspected or confirmed infections in the NHS.

Research recommendations

1. Future trials must include an implementation framework to improve trial intervention fidelity, and repeated cycles of education and training to facilitate implementation of biomarker-guided algorithms into routine clinical care.
2. Future trials should include greater number of DGHs and ensure that they are supported with research nurses and doctors to allow optimal recruitment into RCTs.
3. Future trials should recruit patients earlier in the time course of IV antibiotics to allow for effects of the intervention to be observed.
4. Future trials should ensure that the biomarkers of interest/diagnostics tests are integrated into routine clinical and laboratory workflows.

Conclusions

This trial is timely as it aligns with the current Department of Health Five Year action plan for AMR 2019 to 2024[8] and is a response to research recommendations from two published NICE guidance documents (DG18 and NG15).[7,11]

Chapter 8 Public and patient involvement

Background

The design of this research study was actively sought via the NIHR GenerationR Liverpool YPAG, and Parent and Carer's Research Forum funded by NIHR Alder Hey Clinical Research Facility. Both groups (managed by the PPI lead for BATCH) have worked with several research teams exploring the topic of developing tests to rapidly detect or diagnose SBI in children, including the development of a rapid salivary test to detect SBI in children presenting to the ED (SPICED study), and a study looking at the diagnostic comparison of biomarkers children in ICU (DISTINCTIVE study). Both young people and parents were well aware of the problems associated with diagnosing and treating SBIs 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. Both groups discussed at length the issues associated with AMR and the need to educate young people and families about the misuse of antibiotics. They suggested that findings from this study should be used to inform the cocreation of educational materials for young people, patients and families.

Aims

The purpose of young person and family involvement in this study was to obtain input throughout the study, including input into 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.

Methods

The original plan was to establish a parent advisory group consisting of approximately four to six parents who would work alongside the team and attend Trial Steering Group meetings on a rotational basis. However, for pragmatic reasons, the team decided the best approach would be to continue collaborating with the GenerationR Liverpool YPAG and Parent and Carer's Forum as and when required because of their extensive input to date. The team worked with the groups approximately four times over the course of the study to design the information materials, inform the qualitative phase of the study, and a 28-day follow-up survey aimed at participants of the study. In addition, one parent connected to the trial team based in Cardiff joined the Trial Management Group, and two parents joined the Trial Steering and Data Monitoring Committees, all supported by the PPI lead and research team.

The GenerationR Liverpool YPAG group reviewed the children's information sheets and made suggested changes to the layout and wording, such as having a tri-fold design, making it more colourful and having blue-coloured text. They also helped select the images to be included in the information sheets and suggested having a 'Frequently Asked Questions' section. They liked the logo, consent forms and assent forms.

The parent advisory group were very complimentary on the 28-day follow-up questionnaire, they liked the wording of the instructions and that tick boxes were used to prevent lengthy writing. However, they were concerned that the participants version would not be able to be completed by the children as it was misunderstood that all children would complete the participant version. Therefore, we added to the cover page for clarification that the participant version was only to be completed by children who had consented for themselves (e.g. in the 16- to 18-year-old age range or under the age of 16 with Gillick competency).

A key patient and public involvement and engagement (PPIE) project undertaken as part of the BATCH study was an innovative youth-led drama project to raise awareness of antibiotic resistance with children, families and HCPs. The PPI manager and chief investigator of BATCH received additional funding in 2018 from the University of Liverpool, Knowledge Exchange, Impact and Public Engagement Voucher Scheme to undertake the project. The project commenced in January 2019 and was completed in November 2019.

This project aimed to:

- coproduce and perform a play with young people to teach other children and young people about antibiotic resistance
- assess children and young people's understanding of antibiotic resistance through the medium of drama
- cocreate child-friendly education resources for children, young people, families and teachers about antibiotic resistance.

Activities and outputs during the project:

- *Two script writing workshops* with young people (from the GenerationR Liverpool YPAG and young people from a performing arts school based in a deprived area of Liverpool) and health researchers involved in BATCH. Eight young people from the age group of 8–18 years (7 females, 1 male) attended the first workshop in the Institute in the Park based at Alder Hey Children's Foundation Trust. The second workshop took place in the premises of the performing arts school. Twelve young people attended the workshop aged from 8 to 18 years (11 female, 1 male).
- *Art workshop* with a team at the University of Liverpool School of Engineering and artist in residence to develop artwork for the education materials and publicity flyers to promote the project.
- *A live performance* in Liverpool to celebrate International Clinical Trials Day. Over 60 children, young people, families and HCPs attended the event which involved the performance, and a series of interactive child/family friendly activities focused on the theme of infection and inflammation.
- *A live performance* in front of over 200 primary school-aged children in Liverpool.
- A *recording of the play* shared with primary schools and other youth forums (i.e. youth centres, youth clubs, GenerationR YPAGs across the UK, Girl Guides, etc).
- Cocreating a shortened version of the play in an *animation*, and accompanying education package consisting of surveys, lesson plans, answer sheets, antibiotic facts handout and evaluation forms.

A final report of the project is available at https://jennyprestonblog.files.wordpress.com/2020/03/aa-report-feb-2020.-final.pdf.

Dissemination activities

- The PPI manager invited by the British Society for Antimicrobial Chemotherapy team to join an All-Party Parliamentary Group (APPG) on Antibiotic Resistance meeting at Westminster, which included an awareness raising drop-in event hosted by APPG and the Association of British Pharmaceutical Industry to highlight the work of young people in raising awareness and educating children and families.
- Social media campaigns occurred during antibiotic awareness weeks with one campaign reaching over 28k impressions in 1 week. Campaigns included the following links:
  - YouTube link: https://youtu.be/WKKD2yfDqpE
  - Twitter post: https://twitter.com/Sci_Ani/status/1503323354928984078
  - Facebook post: www.facebook.com/scianimation/videos/927682127921544/
  - LinkedIn post: www.linkedin.com/feed/update/urn:li:activity:6909089207483252736
  - Medium post: https://medium.com/science-animated/how-can-we-win-the-fight-against-antibiotic-resistance-we-need-you-8690ffa9dcb7

- Blogs
  - Blog: Raising awareness of antibiotic resistance with children and young people – Part 1: https://jennyprestonblog.com/2019/02/20/raising-awareness-of-antibiotics-in-children-and-young-people-part-1/
  - Blog: Raising awareness of antibiotic resistance with children and young people – Part 2: https://jennyprestonblog.com/2019/05/17/raising-awareness-of-antibiotics-in-children-and-young-people-part-2/
  - Blog: Raising awareness of antibiotic resistance with children and young people – Part 3: https://jennyprestonblog.com/2020/03/02/raising-awareness-of-antibiotic-resistance-with-children-and-young-people-part-3/

- Blog (GenerationR): Raising awareness of antibiotic resistance with children and young people: https://generationr.org.uk/raising-awareness-of-antibiotic-resistance-with-children-and-young-people/
- Blog (GenerationR): Raising awareness of antibiotic resistance with children and young people – Part 2: https://generationr.org.uk/raising-awareness-of-antibiotic-resistance-with-children-and-young-people-part-2/

Reflective/critical perspective

Members of the BATCH study team showed a commitment to PPIE from the conception of the study idea and throughout the duration of the study. We listened to young people's needs in particular about the importance of raising awareness and educating children and young people about importance health issues, such as antibiotic resistance, and focused our attentions to this task. The chief investigator and PPI manager secured additional funding to deliver this ambitious project, and members of the research team were available during all workshops which really helped when young people had clinical or technical questions that required a direct response.

This unique young person-led project complimented the work undertaken by the PPIE groups and parent involved in the managerial aspects of BATCH via the Trial Management Group. Our key lessons showed that using drama as a means of sharing information and increasing knowledge about health issues with children and young people have many advantages, including making the topic more relevant to children's lives; it generated a conversation and made children consider their own self-management of health care for maybe the first time, and despite the serious nature of the issue, the performance included take-home messages that were delivered in a fun and informative manner.

What did it mean to young people and parents involved in this study?

An evaluation of the drama and education project was undertaken with those who took part as cocreators and performers. On a personal level, the young people felt valued and listened to as the following quotes highlight:

> *I really enjoyed watching the play come to life and gave suggestions to change bits which was included in the final play. I felt like I was important and that all our ideas were took on board and helped write the script. I felt proud to be part of it all.*
> *I really liked the writing workshop at Alder Hey, we got to meet other people from different groups and I felt really important sitting with the Professional Doctors.*

A quote from our parent representative is stated below:

> *As a parent watching the drama with my own child I was encouraged by how education on both antibiotics and resistance to them had enabled a group of young people to create a play that was entertaining but more importantly educational. I believe they created a powerful educational experience that would be beneficial for furthering the awareness of the need for safe and sensible antibiotic usage.*

Chapter 9 Equality, diversity and inclusion

Participant representation

To ensure that our findings are generalisable and applicable to various demographic groups, we designed our research methodology in a pragmatic way to minimise bias and promote inclusivity in participant recruitment.

The 15 recruitment sites chosen for BATCH were purposively spread across the UK including sites in Southern England, Southwest England, Northern England, Northwest England and Wales that allowed for broad geographical representation across socioeconomic backgrounds, ages, ethnicities to ensure diversity within our recruited population.

The baseline demographics of BATCH participants are broadly reflective of the paediatric secondary care population in the UK. BATCH recruited 1949 children aged 72 hours up to 18 years; the median age of participants was 3.1 (IQR 0.7–8.8) years, with 1044 (53.6%) of the sample being male. Around 10% of BATCH participants had non-white ethnicity, which is slightly lower than overall UK population statistics.

Entry criteria were designed to be as inclusive as possible. We promoted the use of NHS language line translation services, and sites kept screening logs which were used to monitor eligible participants who were not recruited due to language barriers (n = 265, 9.1%). We considered translating patient-facing documentation into different languages to aid recruitment; however, as there was a wide variation in the languages spoken, with no language(s) being most commonly used, translation was not undertaken. We plan to develop dissemination materials and videos for promoting the trial results and will translate these into a number of different languages. We will also ensure that patient-facing materials for future studies are as widely accessible as possible and encompass a full range of diversity considerations.

Reflections on your research team and wider involvement

The BATCH research team had substantial PPI in study planning, the funding application, study delivery and dissemination. We were fortunate that our PPI lead and co-applicant is the Senior Patient and Public Involvement Policy Manager at NIHR Alder Hey Clinical Research Facility and University of Liverpool, and we were able to ensure involvement and representation from parent and young people stakeholder groups. Our trial meetings were held as hybrid or online, improving access for those with mobility problems, physical disabilities or those with busy schedules and limited time availability.

Our recruiting centres ranged in size from large children's hospitals to smaller district general hospitals, demonstrating that future paediatric biomarker trials can be conducted in a range of settings. The study training provided to clinical and nursing staff has helped educate and raise awareness of AMS which can be passed onto the next generation of HCPs and researchers.

Additional information

CRediT contribution statement

Cherry-Ann Waldron (https://orcid.org/0000-0001-8465-2492): Data curation (supporting), Funding acquisition (equal), Investigation (supporting), Methodology (equal), Project administration (equal), Resources (equal), Supervision (equal), Visualisation (equal), Writing – original draft (equal), Writing – reviewing and editing (equal).

Philip Pallmann (https://orcid.org/0000-0001-8274-9696): Conceptualisation (equal), Data curation (equal), Formal analysis (lead), Methodology (lead), Project administration (equal), Resources (supporting), Software (lead), Supervision (equal), Validation (lead), Visualisation (equal), Writing – original draft (equal), Writing – reviewing and editing (equal).

Simon Schoenbuchner (https://orcid.org/0000-0003-4892-2170): Data curation (equal), Formal analysis (equal), Methodology (supporting), Software (equal), Validation (equal), Visualisation (supporting), Writing – original draft (equal), Writing – reviewing and editing (supporting).

Debbie Harris (https://orcid.org/0000-0002-7073-7724): Data curation (lead), Formal analysis (supporting), Investigation (equal), Methodology (supporting), Project administration (supporting), Resources (equal), Software (supporting), Validation (supporting), Visualisation (equal), Writing – original draft (equal), Writing – reviewing and editing (supporting).

Lucy Brookes-Howell (https://orcid.org/0000-0002-8263-7130): Conceptualisation (equal), Data curation (lead), Formal analysis (lead), Funding acquisition (supporting), Investigation (lead), Methodology (lead), Project administration (equal), Resources (equal), Software (lead), Supervision (equal), Validation (lead), Visualisation (equal), Writing – original draft (equal), Writing – reviewing and editing (equal).

Céu Mateus (https://orcid.org/0000-0001-6219-219x): Conceptualisation (equal), Data curation (lead), Formal analysis (lead), Funding acquisition (supporting), Methodology (lead), Project administration (equal), Resources (supporting), Software (lead), Supervision (equal), Validation (lead), Visualisation (equal), Writing – original draft (equal), Writing – reviewing and editing (equal).

Jolanta Bernatoniene (https://orcid.org/0009-0005-2941-9125): Conceptualisation (equal), Funding acquisition (supporting), Investigation (equal), Methodology (supporting), Resources (supporting), Visualisation (supporting), Writing – reviewing and editing (supporting).

Katrina Cathie (https://orcid.org/0000-0001-5074-0769): Investigation (equal), Methodology (supporting), Resources (supporting), Visualisation (supporting), Writing – reviewing and editing (supporting).

Saul N Faust (https://orcid.org/0000-0003-3410-7642): Conceptualisation (equal), Funding acquisition (supporting), Investigation (supporting), Methodology (supporting), Resources (supporting), Visualisation (supporting), Writing – reviewing and editing (supporting).

Josie Henley (https://orcid.org/0000-0002-2709-900x): Data curation (supporting), Formal analysis (supporting), Investigation (equal), Methodology (supporting), Resources (supporting), Software (equal), Validation (supporting), Visualisation (equal), Writing – original draft (equal), Writing – reviewing and editing (supporting).

Lucy Hinds (https://orcid.org/0000-0002-5042-4368): Conceptualisation (equal), Funding acquisition (supporting), Investigation (equal), Methodology (supporting), Resources (supporting), Visualisation (supporting), Writing – reviewing and editing (supporting).

Kerry Hood (https://orcid.org/0000-0002-5268-8631): Conceptualisation (equal), Data curation (supporting), Formal analysis (supporting), Funding acquisition (supporting), Methodology (equal), Resources (supporting), Supervision (equal), Visualisation (supporting), Writing – reviewing and editing (supporting).

Chao Huang (https://orcid.org/0000-0002-3627-7218): Conceptualisation (equal), Data curation (supporting), Formal analysis (supporting), Funding acquisition (supporting), Methodology (equal), Resources (supporting), Visualisation (supporting), Writing – reviewing and editing (supporting).

Sarah Jones: Methodology (supporting), Resources (supporting), Other contributions – PPI (supporting), Visualisation (supporting), Writing – reviewing and editing (supporting).

Sarah Kotecha (https://orcid.org/0000-0001-5640-0300): Project administration (supporting), Resources (supporting), Visualisation (supporting), Writing – original draft (equal), Writing – reviewing and editing (supporting).

Sarah Milosevic (https://orcid.org/0000-0003-1973-8286): Data curation (supporting), Formal analysis (supporting), Investigation (equal), Methodology (supporting), Resources (supporting), Software (equal), Validation (supporting), Visualisation (equal), Writing – original draft (supporting), Writing – reviewing and editing (supporting).

Helen Nabwera (https://orcid.org/0000-0003-1056-729x): Investigation (equal), Methodology (supporting), Resources (supporting), Visualisation (supporting), Writing – reviewing and editing (supporting).

Sanjay Patel (https://orcid.org/0000-0001-6329-0496): Conceptualisation (equal), Funding acquisition (supporting), Investigation (supporting), Methodology (supporting), Resources (supporting), Visualisation (supporting), Writing – reviewing and editing (supporting).

Stéphane Paulus (https://orcid.org/0000-0002-0703-9114): Conceptualisation (equal), Funding acquisition (supporting), Investigation (equal), Methodology (supporting), Resources (supporting), Visualisation (supporting), Writing – reviewing and editing (supporting).

Colin VE Powell (https://orcid.org/0000-0001-8181-875x): Conceptualisation (equal), Funding acquisition (supporting), Investigation (supporting), Methodology (supporting), Resources (supporting), Visualisation (supporting), Writing – reviewing and editing (supporting).

Jenny Preston (https://orcid.org/0000-0003-4800-234x): Conceptualisation (equal), Funding acquisition (supporting), Methodology (lead), Other contributions – PPI (lead), Resources (supporting), Visualisation (supporting), Writing – original draft (equal), Writing – reviewing and editing (supporting).

Huasheng Xiang (https://orcid.org/0000-0002-5515-001x): Data curation (supporting), Formal analysis (equal), Methodology (supporting), Software (equal), Validation (supporting), Visualisation (equal), Writing – original draft (equal), Writing – reviewing and editing (supporting).

Emma Thomas-Jones (https://orcid.org/0000-0001-7716-2786): Conceptualisation (equal), Funding acquisition (lead), Investigation (supporting), Methodology (equal), Project administration (equal), Resources (supporting), Supervision (lead), Visualisation (supporting), Writing – reviewing and editing (equal).

Enitan D Carrol (https://orcid.org/0000-0001-8357-7726): Conceptualisation (lead), Data curation (lead), Formal analysis (lead), Funding acquisition (lead), Investigation (lead), Methodology (lead), Project administration (lead), Resources (lead), Supervision (lead), Visualisation (lead), Writing – original draft (lead), Writing – reviewing and editing (lead).

Acknowledgements

Other members of the trial team
We would like to thank and acknowledge the input from the research teams at Alder Hey Children's Hospital, Bristol Royal Hospital for Children, Southampton Children's Hospital, Oxford Children's Hospital, Sheffield Children's Hospital and Noah's Ark Children's Hospital for Wales, including Jenny Whitbread, Daniel Owens, Jenny Pond, Amber Cook, Zoe Oliver, Claire Douglas and Zoe Jordan.

We would like to thank and acknowledge Rachael Hawkins (Clinical Research Facilitator), Judith Evans (Former Research Administrator), Sam Clarkstone (Database Developer), Waku Maboshe (Trial Manager), Mark Goddard (Data Manager) for their contribution to the trial implementation and management; and also, the contribution of Sue Channon, Josie Henley, Sarah Milosevic, Hayley Prout and Kim Smallman in the qualitative study data collection and analysis.

Additional acknowledgements
We would like to thank and acknowledge the support of the Liverpool GenerationR Young Person's Advisory Group, and Biomerieux for their discounted rate for PCT kits and loan of miniVIDAS platforms.

Independent members of the Trial Steering Committee and Independent Data Monitoring Committee
We would like to thank our Trial Steering Committee (TSC) and our independent Data Monitoring Committee (IDMC) for their continued support.

TSC members
Prof Ann Marie Swart (TSC Chairperson, University of East Anglia), Prof Paul Brocklehurst (Former TSC Chairperson, Bangor University), Prof Paul Dark (University of Manchester), Dr Colette Smith, (University College London), Dr Phil Shackley (University of Sheffield) and Kelly Chapman (Patient and Public Involvement Representative).

IDMC members
Prof Graeme MacLennan (IDMC Chairperson, University of Aberdeen), Prof Alastair Sutcliffe (University College London), Prof Philip Howard (University of Leeds) and Danielle Horton Taylor [Patient and Public Involvement Representative, PORT (Paediatric Oncology Reference Team)].

Research networks

We would like to thank the providers of nursing/clinical studies officer and administrative support in all sites. These include staff at the local NIHR Clinical Research Networks and Cardiff and Vale University Health Board Children's Research Unit in Wales.

Recruiting sites
We would like to thank all the staff involved at our participating sites including Principal Investigators, Clinicians, Laboratory Staff, Research Nurses, Research Co-ordinators and Administrators from:

NHS Health Boards in Wales:
Cardiff and Vale University Health Board

Public Health Wales

NHS Trusts in England:

Alder Hey Children's NHS Foundation Trust

Countess of Chester Hospital NHS Foundation Trust

Lewisham and Greenwich NHS Trust

Northern Care Alliance NHS Group

Oxford University Hospitals NHS Foundation Trust

Pennine Acute Hospitals NHS Trust

Portsmouth Hospitals University NHS Trust

Royal Cornwall Hospitals NHS Trust

Royal Devon University Healthcare NHS Foundation Trust

Sheffield Children's NHS Foundation Trust

University Hospitals Bristol and Weston NHS Foundation Trust

University Hospitals Derby and Burton NHS Foundation Trust

University Hospitals Dorset NHS Trust

University Hospital Southampton NHS Foundation Trust

Finally, we would like to thank the children and families who participated, without whom this trial would not have been possible.

Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

This trial had ethical approval granted by an NHS Research Ethics Committee (REC), recognised by the UKECA. The initial approval was granted by the North West Liverpool East REC on 12 April 2018, reference number 18/NW/0100.

Information governance statement

Cardiff University is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, Cardiff University

is the Data Processor; University of Liverpool is the Data Controller, and we process personal data in accordance with their instructions. You can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for the Data Protection Officer here (www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection).

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/MBVA3675.

Primary conflicts of interest: Philip Pallmann is a member of NIHR EME Committee. Colin VE Powell ELVIS Kids study (TSC Member), EASY study (IDSMC Chair). Saul N Faust was Chair of UK NICE Sepsis (2014–6) and Lyme Disease Guidelines (adult and children) (2016–8), was a member of the HTA Commissioning Committee (2018–24) and is a NIHR Senior Investigator. Kerenza Hood is Deputy Chair of NIHR Research Processors panel, a member of HTA Funding Committee Policy group, and was a member of the NIHR HTA General Committee (2016–22) and was a member of NIHR CTU Standing Advisory Committee. Enitan D Carrol was a member of NIHR Invention for Innovation panel (November 2011–3), member of NICE Diagnostic Advisory Committee (April 2014–September 2020), MRC DPFS panel (March 2020–3) and MRC COVID-19 Agile panel (July 2020–1) and is a NIHR Senior Investigator. All other authors declare no competing interests.

The CTR receives funding from Health and Care Research Wales and Cancer Research UK.

Publications

Waldron CA, Thomas-Jones E, Bernatoniene J, Brookes-Howell L, Faust SN, Harris D, *et al.* Biomarker-guided duration of Antibiotic Treatment in Children Hospitalised with confirmed or suspected bacterial infection (BATCH): protocol for a randomised controlled trial. *BMJ Open* 2022;**12**:e047490. https://doi.org/10.1136/bmjopen-2020-047490

Schoenbuchner SM, Huang C, Waldron CA, Thomas-Jones E, Hood K, Carrol ED, *et al.* Biomarker-guided duration of antibiotic treatment in children hospitalised with confirmed or suspected bacterial infection: statistical analysis plan for the BATCH trial and PRECISE sub-study. *Trials* 2023;**24**:364. https://doi.org/10.1186/s13063-022-06956-9

Waldron CA, Pallmann P, Schoenbuchner S, Harris D, Brookes-Howell L, Mateus C, *et al.* Procalcitonin-guided duration of antibiotic treatment in children hospitalised with confirmed or suspected bacterial infection in the UK (BATCH): a pragmatic, multicentre, open-label, two-arm, individually randomised, controlled trial. *Lancet Child Adolesc Health* 2025;**9**:121–30. https://doi.org/10.1016/S2352-4642(24)00306-7

References

1. Waldron CA, Thomas-Jones E, Bernatoniene J, Brookes-Howell L, Faust SN, Harris D, *et al*. Biomarker-guided duration of antibiotic treatment in children hospitalised with confirmed or suspected bacterial infection (BATCH): protocol for a randomised controlled trial. *BMJ Open* 2022;**12**:e047490. https://doi.org/10.1136/bmjopen-2020-047490
2. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, *et al*. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;**315**:801–10. https://doi.org/10.1001/jama.2016.0287
3. Kumar A, Robert D, Wood KE, Light B, Parrillo JE, Sharma S, *et al*. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006;**34**:1589–96. https://doi.org/10.1097/01.CCM.0000217961.75225.E9
4. Fischer JE, Ramser M, Fanconi S. Use of antibiotics in pediatric intensive care and potential savings. *Intensive Care Med* 2000;**26**:959–66. https://doi.org/10.1007/s001340051288
5. Goldmann DA, Weinstein RA, Wenzel RP, Tablan OC, Duma RJ, Gaynes RP, *et al*. Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals. A challenge to hospital leadership. *JAMA* 1996;**275**:234–40. https://doi.org/10.1001/jama.1996.03530270074035
6. Carrol ED, Thomson APJ, Hart CA. Procalcitonin as a marker of sepsis. *Int J Antimicrob Agents* 2002;**20**:1–9. https://doi.org/10.1016/s0924-8579(02)00047-x
7. National Institute for Health and Care Excellence. *Procalcitonin Testing for Diagnosing and Monitoring Sepsis (ADVIA Centaur BRAHMS PCT Assay, BRAHMS PCT Sensitive Kryptor Assay, Elecsys BRAHMS PCT Assay, LIAISON BRAHMS PCT Assay and VIDAS BRAHMS PCT Assay)*. Diagnostics Guidance [DG18]. 7 October 2015. URL: www.nice.org.uk/guidance/dg18 (accessed 11 July 2024).
8. Department of Health. *Tackling Antimicrobial Resistance 2019–2024. The UK's Five-Year National Action Plan. 2019 to 2024*. January 24, 2019. URL: www.gov.uk/government/publications/uk-5-year-action-plan-for-antimicrobial-resistance-2019-to-2024 (assessed 11 July 2024)
9. Department of Health. *Contained and Controlled. The UK's 20-Year Vision for Antimicrobial Resistance*. January 24, 2019. URL: www.gov.uk/government/publications/uk-20-year-vision-for-antimicrobial-resistance (accessed 11 July, 2024)
10. UK Health Security Agency. *Guidance: Start Smart Then Focus: Antimicrobial Stewardship Toolkit for Inpatient Care Settings*. 12 September 2023. URL: www.gov.uk/government/publications/antimicrobial- stewardship-start-smart-then-focus (accessed 11 July, 2024).
11. National Institute for Health and Care Excellence. *Antimicrobial Stewardship: Systems and Processes for Effective Antimicrobial Medicine Use*. NICE Guidelines [NG15]. 18 August 2015. URL: www. nice.org.uk/guidance/ng15 (accessed 11 July 2024).
12. Patel SV, Vergnano S. The impact of paediatric antimicrobial stewardship programmes on patient outcomes. *Curr Opin Infect Dis* 2018;**31**:216–23. https://doi.org/10.1097/QCO.0000000000000449
13. Nielsen MJ, Baines P, Jennings R, Siner S, Kolamunnage-Dona R, Newland P, *et al*. Procalcitonin, C-reactive protein, neutrophil gelatinase-associated lipocalin, resistin and the APTT waveform for the early diagnosis of serious bacterial infection and prediction of outcome in critically ill children. *PLOS One* 2021;**16**:e0246027. https://doi.org/10.1371/journal.pone.0246027
14. Trásy D, Tánczos K, Németh M, Hankovszky P, Lovas A, Mikor A, *et al*.; EProK study group. Early procalcitonin kinetics and appropriateness of empirical antimicrobial therapy in critically ill patients: a prospective observational study. *J Crit Care* 2016;**34**:50–5. https://doi.org/10.1016/j.jcrc.2016.04.007

15. Huang MY, Chen CY, Chien JH, Wu KH, Chang YJ, Wu KH, *et al*. Serum procalcitonin and procalcitonin clearance as a prognostic biomarker in patients with severe sepsis and septic shock. *Biomed Res Int* 2016;**2016**:1758501. https://doi.org/10.1155/2016/1758501

16. Westwood M, Ramaekers B, Whiting P, Tomini F, Joore M, Armstrong N, *et al*. Procalcitonin testing to guide antibiotic therapy for the treatment of sepsis in intensive care settings and for suspected bacterial infection in emergency department settings: a systematic review and cost-effectiveness analysis. *Health Technol Assess* 2015;**19**:1–236. https://doi.org/10.3310/hta19960

17. McMullan BJ, Andresen D, Blyth CC, Avent ML, Bowen AC, Britton PN, *et al*.; ANZPID-ASAP group. Antibiotic duration and timing of the switch from intravenous to oral route for bacterial infections in children: systematic review and guidelines. *Lancet Infect Dis* 2016;**16**:e139–52. https://doi.org/10.1016/S1473-3099(16)30024-X

18. Heren JE, Lund BC, Alexander B, Livorsi DJ. Procalcitonin monitoring and antibiotic duration in presumed lower respiratory tract infections: a propensity score-matched cohort across the veterans health administration. *Open Forum Infect Dis* 2023;**10**:ofad520. https://doi.org/10.1093/ofid/ofad520

19. Scott J, Deresinski S. Use of biomarkers to individualize antimicrobial therapy duration: a narrative review. *Clin Microbiol Infect* 2023;**29**:160–4.

20. Bobillo-Perez S, Sole-Ribalta A, Balaguer M, Esteban E, Girona-Alarcon M, Hernandez-Platero L, *et al*. Procalcitonin to stop antibiotics after cardiovascular surgery in a pediatric intensive care unit – the PROSACAB study. *PLOS One* 2019;**14**:e0220686. https://doi.org/10.1371/journal.pone.0220686

21. Hagedoorn NN, Borensztajn DM, Nijman R, Balode A, von Both U, Carrol ED, *et al*.; PERFORM consortium. Variation in antibiotic prescription rates in febrile children presenting to emergency departments across Europe (MOFICHE): a multicentre observational study. *PLOS Med* 2020;**17**:e1003208. https://doi.org/10.1371/journal.pmed.1003208

22. National Institute for Health and Care Excellence. *Meningitis (Bacterial) and Meningococcal Septicaemia in Under 16s: Recognition, Diagnosis and Management. Clinical guideline [CG102]*. 23 June 2010. URL: www.nice.org.uk/guidance/cg102 (accessed 11 July 2024).

23. Harwood R, Allin B, Jones CE, Whittaker E, Ramnarayan P, Ramanan AV, *et al*.; PIMS-TS National Consensus Management Study Group. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. *Lancet Child Adolesc Health* 2021;**5**:133–41. https://doi.org/10.1016/S2352-4642(20)30304-7

24. Altman DG, Bland JM. Treatment allocation by minimisation. *BMJ* 2005;**330**:843. https://doi.org/10.1136/bmj.330.7495.843

25. Gallagher R, Kirkham JJ, Mason JR, Bird KA, Williamson PR, Nunn AJ, *et al*. Development and inter-rater reliability of the Liverpool adverse drug reaction causality assessment tool. *PLOS One* 2011;**6**:e28096. https://doi.org/10.1371/journal.pone.0028096

26. Generation R. *Young People Improving Research*. URL: https://generationr.org.uk/liverpool (accessed 12 February 2024).

27. Irwin AD, Grant A, Williams R, Ruwanthi Kolamunnage-Dona R, Drew RJ, Paulus S, *et al*. Predicting risk of serious bacterial infections in febrile children in the emergency department. *Pediatrics* 2017;**140**:e20162853. https://doi.org/10.1542/peds.2016-2853

28. de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE, *et al*. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open- label trial. *Lancet Infect Dis* 2016;**16**:819–27. https://doi.org/10.1016/S1473-3099(16)00053-0

29. Paediatric Intensive Care Audit Network (PICANet). *Annual Report: Healthcare Quality Improvement Partnership*. 2015. Paediatric Intensive Care Audit Network. *PICANet Annual Report 2015–2017*. Healthcare Quality Improvement Partnership; 2015.

30. Stevens K. Valuation of the Child Health Utility 9D Index. *PharmacoEconomics* 2012;**30**:729–47. https://doi.org/10.2165/11599120-000000000-00000

31. Gillespie D, Francis NA, Carrol ED, Thomas-Jones E, Butler CC, Hood K. Use of co-primary outcomes for trials of antimicrobial stewardship interventions. *Lancet Infect Dis* 2018;**18**:595–7. https://doi.org/10.1016/S1473-3099(18)30289-5

32. Bustinduy AL, Chis Ster I, Shaw R, Irwin A, Thiagarajan J, Beynon R, *et al*.; CABIN network. Predictors of fever-related admissions to a paediatric assessment unit, ward and reattendances in a South London emergency department: the CABIN 2 study. *Arch Dis Child* 2017;**102**:22–8. https://doi.org/10.1136/archdischild-2016-310494

33. D'Souza S, Guhadasan R, Jennings R, Siner S, Paulus S, Thorburn K, *et al*. Procalcitonin and other common biomarkers do not reliably identify patients at risk for bacterial infection after congenital heart surgery. *Pediatr Crit Care Med* 2019;**20**:243–51. https://doi.org/10.1097/PCC.0000000000001826

34. Offen W, Chuang-Stein C, Dmitrienko A, Littman G, Maca J, Meyerson L, *et al*. Multiple co-primary endpoints: medical and statistical solutions: a report from the Multiple Endpoints Expert Team of the Pharmaceutical Research and Manufacturers of America. *Drug Information J* 2007;**41**:31–46. https://doi.org/10.1177/009286150704100105

35. Schoenbuchner SM, Huang C, Waldron CA, Thomas-Jones E, Hood K, Carrol ED, Pallmann P. Biomarker-guided duration of antibiotic treatment in children hospitalised with confirmed or suspected bacterial infection: statistical analysis plan for the BATCH trial and PRECISE sub-study. *Trials* 2023;**24**:364. https://doi.org/10.1186/s13063-022-06956-9

36. Peugh JL, Strotman D, McGrady M, Rausch J, Kashikar-Zuck S. Beyond intent to treat (ITT): a complier average causal effect (CACE) estimation primer. *J Sch Psychol* 2017;**1**:7–24. https://doi.org/10.1016/j.jsp.2015.12.006

37. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *PLOS Med* 2010;**7**:e1000251. https://doi.org/10.1371/journal.pmed.1000251

38. Piaggio G, Elbourne DR, Pocock SJ, Evans SJW, Altman DG; CONSORT Group. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA* 2012;**308**:2594–604. https://doi.org/10.1001/jama.2012.87802

39. Benjamini Y, Yekutieli D. The control of the false discovery rate in multiple testing under dependency. *Ann Stat* 2001;**29**:1165–88. https://doi.org/10.1214/aos/1013699998

40. Norton EC, Miller MM, Kleinman LC. Computing adjusted risk ratios and risk differences in Stata. *Stata J* 2013;**13**:492–509. https://doi.org/10.1177/1536867X1301300304

41. Quartagno M, Walker AS, Babiker AG, Turner RM, Parmar MKB, Copas A, White IR. Handling an uncertain control group event risk in non-inferiority trials: non-inferiority frontiers and the power-stabilising transformation. *Trials* 2020;**21**:145. https://doi.org/10.1186/s13063-020-4070-4

42. Tchetgen Tchetgen EJ. Identification and estimation of survivor average causal effects. *Stat Med* 2014;**33**:3601–28. https://doi.org/10.1002/sim.6181

43. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, *et al*. Process evaluation of complex interventions: medical research council guidance. *BMJ* 2015;**350**:h1258. https://doi.org/10.1136/bmj.h1258

44. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M; Medical Research Council Guidance. Developing and evaluating complex interventions: the new medical research council guidance. *BMJ* 2008;**337**:a1655. https://doi.org/10.1136/bmj.a1655

45. 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 Feasibility Stud* 2015;**1**:1–13. https://doi.org/10.1186/s40814-015-0026-y

46. Ritchie J, Lewis J. *Qualitative Research Practice: A Guide for Social Science Students and Researchers*. London: Sage Publications; 2003.

47. Gale NK, 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. https://doi.org/10.1186/1471-2288-13-117

48. Turner D, Hammerman C, Rudensky B, Schlesinger Y, Goia C, Schimmel MS. Procalcitonin in preterm infants during the first few days of life: introducing an age related nomogram. *Arch Dis Child Fetal Neonatal Ed* 2006;**91**:F283–6. https://doi.org/10.1136/adc.2005.085449

49. Krasteva M, Karastaneva A, Besheva M, Deneva T, Davcheva D. Dynamics in levels of procalcitonin in healthy term newborns during the first 24 hours of life. *Akush Ginekol (Sofiia)* 2013;**52**:23–8.

50. Liu Y-F, Tong X-M, Zheng F-Y, Piao M-H, Ning Y-Z. Physiological changes in serum procalcitonin concentrations in premature infants early after birth. *Zhongguo Dang Dai Er Ke Za Zhi* 2013;**15**:81–4.

51. Assumma M, Signore F, Pacifico L, Rossi N, Osborn JF, Chiesa C. Serum procalcitonin concentrations in term delivering mothers and their healthy offspring: a longitudinal study. *Clin Chem* 2000;**46**:1583–7.

52. Liu C, Fang C, Xie L. Diagnostic utility of procalcitonin as a biomarker for late-onset neonatal sepsis. *Transl Pediatr* 2020;**9**:237–42. https://doi.org/10.21037/tp-20-127

53. Sugitharini V, Prema A, Thangam EB. Inflammatory mediators of systemic inflammation in neonatal sepsis. *Inflamm Res* 2013;**62**:1025–34. https://doi.org/10.1007/s00011-013-0661-9

54. Auriti C, Fiscarelli E, Ronchetti MP, Argentieri M, Marrocco G, Quondamcarlo A, *et al*. Procalcitonin in detecting neonatal nosocomial sepsis. *Arch Dis Child Fetal Neonatal Ed* 2012;**97**:F368–70. https://doi.org/10.1136/fetalneonatal-2010-194100

55. Altunhan H, Annagür A, Örs R, Mehmetoğlu I. Procalcitonin measurement at 24 hours of age may be helpful in the prompt diagnosis of early-onset neonatal sepsis. *Int J Infect Dis* 2011;**15**:e854–8. https://doi.org/10.1016/j.ijid.2011.09.007

56. Mussap M, Degrandi R, Cataldi L, Fanos V, Plebani M. Biochemical markers for the early assessment of neonatal sepsis: the role of procalcitonin. *J Chemother* 2007;**19**:35–8. https://doi.org/10.1080/1120009x.2007.11782442

57. Mo Y, Lim C, Watson JA, White NJ, Cooper BS. Non-adherence in non-inferiority trials: pitfalls and recommendations. *BMJ* 2020;**370**:m2215. https://doi.org/10.1136/bmj.m2215

58. Frick KD. Microcosting quantity data collection methods. *Med Care* 2009;**47**:S76–81. https://doi.org/10.1097/mlr.0b013e31819bc064

59. Improving Antimicrobial Prescribing Group. *Serum Procalcitonin Testing in Medical Admissions (for Adults Only)*. 2017. URL: www.lhp.leedsth.nhs.uk/detail.aspx?ID=5057 (accessed 26 June 2023)

60. Faria R, Gomes M, Epstein DH, White IR. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. *PharmacoEconomics* 2014;**32**:1157–70. https://doi.org/10.1007/s40273-014-0193-3

61. Royston P. ICE: Stata module for multiple imputation of missing values. *Statistical Software Components S446602, Boston College Department of Economics;* revised 25 October 2014.

62. Office of National Statistics. *Employee Earnings in the UK: 2021*. 26 October 2021. URL: www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours/bulletins/annualsurveyofhoursandearnings/2021 (accessed 26 November 2024).

63. Bhandari A, Wagner T. Self-reported utilization of health care services: improving measurement and accuracy. *Med Care Res Rev* 2006;**63**:217–35. https://doi.org/10.1177/1077558705285298

64. Petrou S, Murray L, Cooper P, Davidson LL. The accuracy of self-reported healthcare resource utilization in health economic studies. *Int J Technol Assess Health Care* 2002;**18**:705–10. https://doi.org/10.1017/s026646230200051x

65. Damschroder LJ, Reardon CM, Widerquist MAO, Lowery J. The updated consolidated framework for implementation research based on user feedback. *Implement Sci* 2022;**17**:75. https://doi.org/10.1186/s13012-022-01245-0

66. Braun V, Clarke V. What can 'thematic analysis' offer health and wellbeing researchers? *Int J Qual Stud Health Well-being* 2014;**9**:26152. https://doi.org/10.3402/qhw.v9.26152

67. Tonkin-Crine S, Sibyl Anthierens S, Hood K, Yardley L, Cals JWL, Francis NA, *et al*. Discrepancies between qualitative and quantitative evaluation of randomised controlled trial results: achieving clarity through mixed methods triangulation. *Implement Sci* 2016;**11**:66. https://doi.org/10.1186/s13012-016-0436-0

68. Department of Health and Social Care. *Antimicrobial Resistance Poses 'Catastrophic Threat', Says Chief Medical Officer*. Press release 12 March 2013

69. Stocker M, van Herk W, El Helou S, Dutta S, Fontana MS, Schuerman FABA, *et al*.; NeoPInS Study Group. Procalcitonin-guided decision making for duration of antibiotic therapy in neonates with suspected early-onset sepsis: a multicentre, randomised controlled trial (NeoPIns). *Lancet* 2017;**390**:871–81. https://doi.org/10.1016/S0140-6736(17)31444-7

70. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, *et al*.; PRORATA trial group. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet* 2010;**375**:463–74. https://doi.org/10.1016/S0140-6736(09)61879-1

71. Elnajdy D, El-Dahiyat F. Antibiotics duration guided by biomarkers in hospitalized adult patients; a systematic review and meta-analysis. *Infect Dis* 2022;**54**:387–402. https://doi.org/10.1080/23744235.2022.2037701

72. Papp M, Kiss N, Baka M, Trásy D, Zubek L, Fehérvári P, *et al*. Procalcitonin-guided antibiotic therapy may shorten length of treatment and may improve survival – a systematic review and meta-analysis. *Crit Care* 2023;**27**:394. https://doi.org/10.1186/s13054-023-04677-2

73. Vergnano S, Bamford A, Bandi S, Chappel F, Demirjian A, Doerholt K, *et al*. Paediatric antimicrobial stewardship programmes in the UK's regional children's hospitals. *J Hosp Infect* 2020;**105**:736–40. https://doi.org/10.1016/j.jhin.2020.05.030

74. McMullan BJ, Bryant PA, Duffy E, Bielicki J, De Cock P, Science M, *et al*. Multinational consensus antimicrobial stewardship recommendations for children managed in hospital settings. *Lancet Infect Dis* 2023;**23**:e199–207. https://doi.org/10.1016/S1473-3099(22)00726-5

75. Euden J, Thomas-Jones E, Aston S, Brookes-Howell L, Carman J, Carrol ED, *et al*.; PRONTO team. PROcalcitonin and NEWS2 evaluation for Timely identification of sepsis and Optimal use of antibiotics in the emergency department (PRONTO): protocol for a multicentre, open-label, randomised controlled trial. *BMJ Open* 2022;**12**:e063424. https://doi.org/10.1136/bmjopen-2022-063424

76. Dark P, Perkins GD, McMullan R, McAuley D, Gordon AC, Clayton J, *et al*. BiomArker-guided Duration of Antibiotic treatment in hospitalised Patients with suspecTed Sepsis (ADAPT-Sepsis): a protocol for a multicentre randomised controlled trial. *J Intensive Care Soc* 2023;**24**:427–34. https://doi.org/10.1177/17511437231169193

77. Turner R, Hart J, Ashiru-Oredope D, Atkins L, Eades C, Felton T, *et al*. A qualitative interview study applying the COM-B model to explore how hospital-based trainers implement antimicrobial stewardship education and training in UK hospital-based care. *BMC Health Serv Res* 2023;**23**:770. https://doi.org/10.1186/s12913-023-09559-5

Appendix 1 Post hoc derivation of primary and secondary duration outcomes

After completion of trial data collection, it was found that data on the start and stop times of antibiotic use were only collected per antibiotic, and not per patient. It was therefore not possible to derive durations by simply comparing start and stop times as planned. Discussion with the chief investigator revealed that gaps of up to 48 hours between antibiotics do not necessarily indicate clinical decisions to stop and restart, so merging overlapping antibiotics would not solve this discrepancy. In an effort to remain as close as possible to the planned analysis, we used the following heuristic algorithm to derive antibiotic duration outcomes:

1. Drop medications that are not antibiotics.
2. Drop antibiotics that were stopped before randomisation.
3. Limit analysis to relevant antibiotics:
    a. Primary analysis: keep IV antibiotics.
    b. Secondary analysis: keep all antibiotics.
    c. Secondary analysis: keep broad-spectrum antibiotics.

4. Estimate the 'minimum interval' of antibiotic use for each patient:
    a. If stop time is missing, assume it was 00 : 00 on the stop date (or the start time, if known and later).
    b. If start time is missing, assume it was 23 : 59 on the start date (or the stop time, if earlier).
    c. Merge intervals until there is a gap of more than 12 hours. Drop subsequent intervals.

5. Estimate 'maximum interval' of antibiotic use for each patient:
    a. If stop time is missing, assume it was 23 : 59 on the stop date.
    b. If start time is missing, assume it was 00 : 00 on the start date.
    c. Merge intervals until there is a gap of more than 48 hours. Drop subsequent intervals.

6. Calculate duration:
    a. If the patient received no relevant antibiotics (as per step 3), then duration is 0.
    b. If the maximum interval of antibiotic use does not overlap with the date of randomisation, then duration is 0.
    c. If the minimum and maximum intervals are the same, then duration is assumed to be known (i.e. not censored).
    d. If the minimum and maximum durations are different, then duration is unknown (i.e. right-censored at the minimum duration).

Appendix 2 Price and unit costs for antibiotics

List of antibiotic	Quantity	Unit	Basic price (£)	Unit price (£)	Source
Aciclovir 200 mg/5 ml oral suspension sugar free	5000	mg	35.78	0.007156	NHS Electronic Drug Tariff 2023
Aciclovir 250 mg/10 ml concentrate for solution for infusion vials	2500	mg	50.00	0.020000	NHS Electronic Drug Tariff 2023
Amikacin 500 mg/2 ml solution for injection vials	2500	mg	60.00	0.024000	NICE British National Formulary (BNF) April 2023
Amoxicillin 125 mg/5 ml oral suspension	100	ml	2.29	0.022900	NHS Electronic Drug Tariff 2023
Amoxicillin 250 mg/5 ml oral suspension	100	ml	2.88	0.028800	NHS Electronic Drug Tariff 2023
Amoxicillin 500 mg powder for solution for injection vials	5000	mg	9.60	0.001920	NHS Electronic Drug Tariff 2023
Amoxicillin 500 mg/5 ml oral suspension sugar free	500	mg	3.50	0.007000	NHS Electronic Drug Tariff 2023
Amphotericin B 50 mg powder for solution for infusion vials	50	mg	16.21	0.324200	NHS Electronic Drug Tariff 2023
Aprokam 50 mg powder for solution for injection vials	500	mg	49.95	0.099900	NICE British National Formulary (BNF) April 2023
Azactam 2 g powder for solution for injection vials	2000	mg	18.82	0.009410	NICE British National Formulary (BNF) April 2023
Azithromycin 200 mg/5 ml oral suspension	600	mg	4.06	0.006767	NHS Electronic Drug Tariff 2023
Azithromycin 500 mg powder for concentrate for solution for infusion vials	500	mg	9.50	0.019000	NICE British National Formulary (BNF) April 2023
Benzylpenicillin 1.2 g powder for solution for injection vials	30,000	mg	109.50	0.003650	NHS Electronic Drug Tariff 2023
Benzylpenicillin 600 mg powder for solution for injection vials	1200	mg	5.90	0.004917	NHS Electronic Drug Tariff 2023
Cefaclor 125 mg/5 ml oral suspension	2500	mg	4.13	0.001652	NHS Electronic Drug Tariff 2023
Cefalexin 250 mg/5 ml oral suspension	5000	mg	3.85	0.000770	NHS Electronic Drug Tariff 2023
Cefixime 200 mg tablets	1400	mg	13.23	0.009450	NHS Electronic Drug Tariff 2023
Cefotaxime 500 mg powder for solution for injection vials	5000	mg	30.00	0.006000	NICE British National Formulary (BNF) April 2023
Ceftazidime 500 mg powder for solution for injection vials	500	mg	4.25	0.008500	NICE British National Formulary (BNF) April 2023
Ceftriaxone 250 mg powder for solution for injection vials	250	g	2.40	0.009600	NHS Electronic Drug Tariff 2023
Cefuroxime 1.5 g powder for solution for injection vials	15,000	mg	50.50	0.003367	NICE British National Formulary (BNF) April 2023
Cefuroxime 125 mg/5 ml oral suspension	1750	mg	5.20	0.002971	NHS Electronic Drug Tariff 2023
Chloramphenicol 0.5% eye drops	10	ml	9.53	0.953000	NHS Electronic Drug Tariff 2023
Cidofovir 375 mg/5 ml concentrate for solution for infusion vials	375	mg	1100.00	2.933333	NICE British National Formulary (BNF) April 2023
Ciprofloxacin 200 mg/100 ml solution for infusion bottles	2000	mg	157.40	0.078700	NICE British National Formulary (BNF) April 2023
Ciprofloxacin 250 mg/5 ml oral suspension	5000	mg	21.29	0.004258	NHS Electronic Drug Tariff 2023

List of antibiotic	Quantity	Unit	Basic price (£)	Unit price (£)	Source
Ciprofloxacin 2 mg/ml ear drops 0.25 ml unit dose preservative free	3.75	ml	6.01	1.602667	NHS Electronic Drug Tariff 2023
Clarithromycin 125 mg/5 ml oral suspension	1750	mg	3.48	0.001989	NHS Electronic Drug Tariff 2023
Clarithromycin 500 mg powder for solution for infusion vials	500	mg	9.45	0.018900	NHS Electronic Drug Tariff 2023
Clindamycin 300 mg/2 ml solution for injection ampoules	1500	mg	31.01	0.020673	NICE British National Formulary (BNF) April 2023
Clindamycin 75 mg capsules	1800	mg	7.45	0.004139	NHS Electronic Drug Tariff 2023
Clotrimazole 1% cream	20	g	1.37	0.068500	NHS Electronic Drug Tariff 2023
Clotrimazole 1% cream	50	g	3.43	0.068600	NHS Electronic Drug Tariff 2023
Co-amoxiclav 125 mg/31 mg/5 ml oral suspension	100	ml	5.00	0.050000	NHS Electronic Drug Tariff 2023
Co-amoxiclav 250 mg/125 mg tablets	21	Tablet	1.96	0.093333	NHS Electronic Drug Tariff 2023
Co-amoxiclav 400 mg/57 mg/5 ml oral suspension sugar free	35	ml	4.13	0.118000	NHS Electronic Drug Tariff 2023
Co-amoxiclav 500 mg/100 mg powder for solution for injection vials	6000	mg	13.50	0.002250	NICE British National Formulary (BNF) April 2023
Co-amoxiclav 500 mg/100 mg powder for solution for injection vials	6	g	13.50	2.250000	NICE British National Formulary (BNF) April 2023
Co-amoxiclav 500 mg/125 mg tablets	21	Tablet	4.39	0.209048	NHS Electronic Drug Tariff 2023
Doxycycline 50 mg capsules	1400	mg	1.49	0.001064	NHS Electronic Drug Tariff 2023
Erythromycin ethyl succinate 250 mg/5 ml oral suspension	5000	mg	10.27	0.002054	NHS Electronic Drug Tariff 2023
Flucloxacillin 250 mg powder for solution for injection vials	2500	mg	8.60	0.003440	NHS Electronic Drug Tariff 2023
Flucloxacillin 250 mg/5 ml oral solution	5000	mg	3.27	0.000654	NHS Electronic Drug Tariff 2023
Fluconazole 50 mg/25 ml solution for infusion vials	50	mg	20.00	0.400000	NHS Electronic Drug Tariff 2023
Fluconazole 50 mg/5 ml oral suspension	350	mg	28.41	0.081171	NHS Electronic Drug Tariff 2023
Gentamicin 20 mg/2 ml solution for injection ampoules	100	mg	11.25	0.112500	NHS Electronic Drug Tariff 2023
Gentamicin 20 mg/2 ml solution for injection vials	100	mg	11.25	0.112500	NHS Electronic Drug Tariff 2023
Levofloxacin 250 mg tablets	2500	mg	8.19	0.003276	NHS Electronic Drug Tariff 2023
Linezolid 100 mg/5 ml oral suspension	3000	mg	222.50	0.074167	NHS Electronic Drug Tariff 2023
Meropenem 500 mg powder for solution for injection vials	5000	mg	112.10	0.022420	NHS Electronic Drug Tariff 2023
Metronidazole 200 mg/5 ml oral suspension	4000	mg	62.50	0.015625	NHS Electronic Drug Tariff 2023
Metronidazole 500 mg/100 ml infusion 100 ml bags	10,000	ml	71.85	0.007185	NHS Electronic Drug Tariff 2023
Micafungin 50 mg powder for concentrate for solution for infusion vials	50	mg	196.08	3.921600	NICE British National Formulary (BNF) April 2023
Promixin 1 million unit powder for nebuliser solution unit dose vials	30	mu	204.00	6.800000	NICE British National Formulary (BNF) April 2023

Appendix 3 Price and unit costs for additional medication prescribed listed in the follow-up questionnaire

Medication name	Quantity	Unit	Basic price (£)	Unit price (£)	Source
Abidec Multivitamin Oral Drops	25	ml	7.1	0.284000	Boots
Aciclovir 200 mg/5 ml oral suspension sugar free	5000	mg	35.78	0.007156	NHS Electronic Drug Tariff 2023
Acitretin	600	mg	30.42	0.050700	NICE British National Formulary (BNF) April 2023
ActivHeal Alginate dressing 10 cm x 10 cm	10	Unit	15.87	1.587000	Lowdham Pharmacy
Adrenaline 1 : 1000 1 mg/1 ml	150	mg	53.8	0.358667	NICE British National Formulary (BNF) April 2023
Adrenaline EpiPen 1 : 2000	150	mg	53.8	0.358667	NICE British National Formulary (BNF) April 2023
Alfacalcidol	15,000	ng	9.9	0.000660	NICE British National Formulary (BNF) April 2023
Alimemazine tartrate oral suspension	200	mg	182	0.910000	NICE British National Formulary (BNF) April 2023
Alpha tocopheryl oral suspension	10,000	mg	76.81	0.007681	NICE British National Formulary (BNF) April 2023
Amitriptyline 10 mg/5 ml oral solution sugar	300	mg	136.47	0.454900	NICE British National Formulary (BNF) April 2023
Amlodipine 5 mg/5 ml oral suspension sugar free	150	ml	70	0.466667	NICE British National Formulary (BNF) April 2023
Amoxicillin 125 mg/5 ml oral suspension	100	ml	2.29	0.022900	NHS Electronic Drug Tariff 2023
Amoxicillin 500 mg/5 ml oral suspension sugar free	500	mg	3.5	0.007000	NHS Electronic Drug Tariff 2023
Anakinra injection	700	mg	183.61	0.262300	NICE British National Formulary (BNF) April 2023
Aspirin 75 mg	7500	mg	1.99	0.000265	Boots
Azithromycin 200 mg/5 ml oral suspension	600	mg	4.06	0.006767	NHS Electronic Drug Tariff 2023
Azithromycin 500 mg powder for concentrate for solution for infusion vials	500	mg	9.5	0.019000	NICE British National Formulary (BNF) April 2023
Baclofen oral solution	300	mg	4.22	0.014067	NICE British National Formulary (BNF) April 2023
Beclametasone 50 µg/dose inhaler	10,000	mg	3.7	0.000370	NICE British National Formulary (BNF) April 2023
Benzydamine 0.15% oromucosal spray sugar free	30	ml	3.01	0.100333	NICE British National Formulary (BNF) April 2023
Betamethasone 0.1% drops solution	10	ml	2.32	0.232000	NICE British National Formulary (BNF) April 2023
Bio-Kult Advanced Multi-Strain Digestive System Formulation	30	Capsule	10.49	0.349667	Holland & Barrett

Medication name	Quantity	Unit	Basic price (£)	Unit price (£)	Source
Bisacodyl 10 mg suppositories	120	mg	2.77	0.023083	NICE British National Formulary (BNF) April 2023
Bisoprolol 5 mg tablets	140	mg	0.75	0.005357	NICE British National Formulary (BNF) April 2023
Calpol Infant 120 mg/5 ml oral suspension	1440	mg	2.83	0.001965	NICE British National Formulary (BNF) April 2023
Captopril 5 mg/5 ml oral solution sugar free	100	mg	93.82	0.938200	NICE British National Formulary (BNF) April 2023
Carbamazepine 100 mg/5 ml oral suspension sugar free	300	ml	9.69	0.032300	NICE British National Formulary (BNF) April 2023
Carvedilol	87.5	mg	0.79	0.009029	NICE British National Formulary (BNF) April 2023
Cefaclor 125 mg/5 ml oral suspension	2500	mg	4.13	0.001652	NHS Electronic Drug Tariff 2023
Cefalexin 250 mg/5 ml oral suspension	5000	mg	3.85	0.000770	NHS Electronic Drug Tariff 2023
Ceftriaxone	250	g	2.4	0.009600	NHS Electronic Drug Tariff 2023
Cetraben cream	50	ml	6.05	0.121000	Boots
Chloral hydrate	20,000	mg	162.83	0.008142	NICE British National Formulary (BNF) April 2023
Chloramphenamine	60	mg	2.21	0.036833	NICE British National Formulary (BNF) April 2023
Chloramphenicol 0.5% eye drops	10	ml	9.53	0.953000	NHS Electronic Drug Tariff 2023
Chlorhexidine gluconate 0.2% mouthwash	300	ml	2.24	0.007467	NICE British National Formulary (BNF) April 2023
Chlorhexidine gluconate 40 mg/1 ml	125	ml	1.72	0.013760	NICE British National Formulary (BNF) April 2023
Ciprofloxacin 0.3% eye drops	5	ml	4.7	0.940000	NICE British National Formulary (BNF) April 2023
Ciprofloxacin 2 mg/ml ear drops 0.25 ml unit dose	15	Unit	6.01	0.400667	NICE British National Formulary (BNF) April 2023
Ciprofloxacin 50 mg per 1 ml	25,000	mg	21.29	0.000852	NICE British National Formulary (BNF) April 2023
Clarithromycin 250 mg/5 ml oral suspension	3500	mg	5	0.001429	NHS Electronic Drug Tariff 2023
Clenil Modulite inhaler	50	mg	16.99	0.339800	Pharmacy4u
Clindamycin 150 mg capsules	3600	mg	2.8	0.000778	NHS Electronic Drug Tariff 2023
Clindamycin 75 mg capsules	1800	mg	7.45	0.004139	NHS Electronic Drug Tariff 2023
Clobavate 0.05%	30	g	1.49	0.049667	NICE British National Formulary (BNF) April 2023
Clobazam 5 mg/5 ml oral suspension sugar free	150	mg	87.46	0.583067	NICE British National Formulary (BNF) April 2023
Clonazepam 500 µg/5 ml oral solution sugar free	15,000	mg	77.09	0.005139	NICE British National Formulary (BNF) April 2023
Clonidine 50 µg/5 ml oral solution sugar free	1000	mg	172.73	0.172730	NICE British National Formulary (BNF) April 2023
Clopidogrel 75 mg	2250	mg	1.24	0.000551	NICE British National Formulary (BNF) April 2023

Medication name	Quantity	Unit	Basic price (£)	Unit price (£)	Source
Clotrimazole 1% cream	20	g	1.46	0.073000	NICE British National Formulary (BNF) April 2023
Co-amoxiclav 125 mg/31 mg/5 ml oral suspension	100	ml	5	0.050000	NHS Electronic Drug Tariff 2023
Co-amoxiclav 250 mg/62 mg/5 ml oral suspension	100	ml	5	0.050000	NHS Electronic Drug Tariff 2023
Co-amoxiclav 500 mg/125 mg tablets	21	Tablet	4.39	0.209048	NHS Electronic Drug Tariff 2023
Colecalciferol 1000 unit/1 ml	30	ml	4.5	0.150000	NICE British National Formulary (BNF) April 2023
Colistimethate 2 million unit powder for solution for injection vials	10	ml	32.4	3.240000	NHS Electronic Drug Tariff 2023
Co-trimoxazole 40 mg/200 mg/5 ml oral suspension sugar free	4800	mg	9.96	0.002075	NICE British National Formulary (BNF) April 2023
Co-trimoxazole 80 mg/400 mg tablets	28	Tablet	1.73	0.061786	NICE British National Formulary (BNF) April 2023
Cyclopentolate hydrochloride 0.5% eye drops	20	Unit	12.58	0.629000	NICE British National Formulary (BNF) April 2023
Daktacort Hydrocortisone Cream	15	g	6.99	0.466000	Chemist4u
Dalivit Multivitamin Oral Drops	25	ml	11.99	0.479600	Chemist4u
Dalteparin sodium 2500 unit/1 ml	100,000	Unit	51.22	0.000512	NICE British National Formulary (BNF) April 2023
Dermol 500 lotion	500	ml	8.99	0.017980	Chemist4u
Desmopressin	750	mg	15.16	0.020213	NICE British National Formulary (BNF) April 2023
Dexamethasone 2 mg/5 ml oral solution sugar free	150	ml	42.3	0.282000	NICE British National Formulary (BNF) April 2023
Diclofenac sodium 25 mg	700	mg	4.13	0.005900	NICE British National Formulary (BNF) April 2023
Difflam Spray 30 ml	30	ml	8.7	0.290000	Boots
Dihydrocodeine	840	mg	2.21	0.002631	NICE British National Formulary (BNF) April 2023
Doxycycline 50 mg capsules	1400	mg	1.49	0.001064	NHS Electronic Drug Tariff 2023
Enalapril maleate	28	Tablet	7.87	0.281071	NICE British National Formulary (BNF) April 2023
Enoxaparin sodium 100 mg/1 ml	200	mg	20.86	0.104300	NICE British National Formulary (BNF) April 2023
Epimax Ointment 500g	500	g	5.46	0.010920	ExpressChemist
Erythromycin ethyl succinate 125 mg/5 ml oral suspension	100	ml	5.91	0.059100	NICE British National Formulary (BNF) April 2023
Esomeprazole 40 mg powder for solution for injection vials	40	mg	4.25	0.106250	NICE British National Formulary (BNF) April 2023
Factor VIII fraction, dried	1500	Unit	1275	0.850000	NICE British National Formulary (BNF) April 2023
Feredet 190 mg/5 ml oral solution	200	ml	4.89	0.024450	NICE British National Formulary (BNF) April 2023

Medication name	Quantity	Unit	Basic price (£)	Unit price (£)	Source
Ferrous fumarate 28 mg/1 ml	5600	mg	3.37	0.000602	NICE British National Formulary (BNF) April 2023
Flucloxacillin 250 mg/5 ml oral solution	5000	mg	3.27	0.000654	NHS Electronic Drug Tariff 2023
Fluconazole 10 mg/1 ml	350	mg	28.41	0.081171	NICE British National Formulary (BNF) April 2023
Folic acid 500 µg/1 ml	150	ml	9.16	0.061067	NICE British National Formulary (BNF) April 2023
Forceval Multivitamin	15	Capsule	9.39	0.626000	Chemist4u
Fosfomycin 2 g	20	g	150	7.500000	NICE British National Formulary (BNF) April 2023
Furosemide 4 mg/1 ml	600	mg	14.81	0.024683	NICE British National Formulary (BNF) April 2023
Fusidic acid 20 mg/1 g	15	g	2.35	0.156667	NICE British National Formulary (BNF) April 2023
Gabapentin 50 mg/1 ml	7500	mg	65.24	0.008699	NICE British National Formulary (BNF) April 2023
Gaviscon	500	ml	6.99	0.013980	Chemist4u
Glycerol 2 g suppositories	12	sup	3.31	0.275833	NICE British National Formulary (BNF) April 2023
Glycopyrronium bromide 1 mg/5 ml oral solution sugar free	30	mg	104.01	3.467000	NICE British National Formulary (BNF) April 2023
Hydrocortisone 1% w/w cream	15	g	2.83	0.188667	NICE British National Formulary (BNF) April 2023
Hydrocortisone 2.5 mg tablets	75	mg	20.77	0.276933	NICE British National Formulary (BNF) April 2023
Hydromol ointment	500	g	9.29	0.018580	Chemist4u
Hydromoor 0.3% eye drops	30	Unit	5.89	0.196333	NICE British National Formulary (BNF) April 2023
Ibuprofen	50,000	mg	9.3	0.000186	NICE British National Formulary (BNF) April 2023
Instant Carobel	135	g	6.95	0.051481	NutriDrinks
Insulin aspart 100 unit/1 ml	100	Unit	14.08	0.140800	NICE British National Formulary (BNF) April 2023
Kay-Cee-L syrup	500	ml	10.15	0.020300	NICE British National Formulary (BNF) April 2023
Lactobacillus	60	Capsule	8.99	0.149833	Holland & Barrett
Lactulose oral solution	300	ml	2.47	0.008233	NICE British National Formulary (BNF) April 2023
Lansoprazole	840	mg	1.17	0.001393	NICE British National Formulary (BNF) April 2023
Levetiracetam oral solution	15,000	mg	23.3	0.001553	NICE British National Formulary (BNF) April 2023
Levomepromazine 25 mg/ml solution for injection	250	mg	20.13	0.080520	NICE British National Formulary (BNF) April 2023
Levothyroxine	500	mg	94.99	0.189980	NICE British National Formulary (BNF) April 2023

Medication name	Quantity	Unit	Basic price (£)	Unit price (£)	Source
Lidocaine 100 mg/10 ml (1%) solution for injection	200	ml	12.62	0.063100	NICE British National Formulary (BNF) April 2023
Linezolid oral suspension	15000	mg	222.5	0.014833	NICE British National Formulary (BNF) April 2023
Loperamide tablets	60	mg	2.17	0.036167	NICE British National Formulary (BNF) April 2023
Mebendazole 100 mg/5 ml oral suspension	30	ml	1.55	0.051667	NICE British National Formulary (BNF) April 2023
Melatonin	60	mg	15.3	0.255000	NICE British National Formulary (BNF) April 2023
Metoclopramide 10 mg/2 ml solution for injection	50	mg	5	0.100000	NICE British National Formulary (BNF) April 2023
Metronidazole 200 mg/5 ml oral suspension	20,000	mg	62.36	0.003118	NICE British National Formulary (BNF) April 2023
Miconazole cream	15	g	3.14	0.209333	NICE British National Formulary (BNF) April 2023
Midazolam hydrochloride	40	mg	91.5	2.287500	NICE British National Formulary (BNF) April 2023
Morphine sulphate 10 mg/5 ml oral solution	1000	mg	1.5	0.001500	NICE British National Formulary (BNF) April 2023
Movicol Powder Sachets	20	Sachet	9.99	0.499500	NICE British National Formulary (BNF) April 2023
Moxifloxacin 400 mg tablets	2000	mg	6.9	0.003450	NICE British National Formulary (BNF) April 2023
Multivitamin Gummy	30	Chewable	4.99	0.166333	Holland & Barrett
Mupirocin 2% nasal ointment	3	g	4.24	1.413333	NICE British National Formulary (BNF) April 2023
Naprosyn 250 mg tablets	14,000	mg	4.29	0.000306	NICE British National Formulary (BNF) April 2023
Nitrofurantoin 25 mg/5 ml oral suspension sugar free	300	ml	449.26	1.497533	NICE British National Formulary (BNF) April 2023
Nutricia monogeny	400	g	32.45	0.081125	NutriDrinks
Nutricia Fortisip Compact	4	Bottle	10.09	2.522500	Chemist4u
Nystatin 100,000 units/ml oral suspension	30	ml	1.8	0.060000	NICE British National Formulary (BNF) April 2023
Omeprazole 10 mg tablets	280	mg	9.3	0.033214	NICE British National Formulary (BNF) April 2023
Omeprazole 10 mg/5 ml oral suspension sugar free	150	mg	124	0.826667	NICE British National Formulary (BNF) April 2023
Oseltamivir 6 mg/ml oral suspension	390	mg	10.27	0.026333	NICE British National Formulary (BNF) April 2023
Paracetamol 500 mg/5 ml oral suspension sugar free	15,000	mg	29.7	0.001980	NICE British National Formulary (BNF) April 2023
Parenteral nutrition	10	ml	3.55	0.355000	NICE British National Formulary (BNF) April 2023
Phenoxymethylpenicillin 125 mg/5 ml oral solution	2500	mg	2.31	0.000924	NHS Electronic Drug Tariff 2023

Medication name	Quantity	Unit	Basic price (£)	Unit price (£)	Source
Phenoxymethylpenicillin 250 mg tablets	7000	mg	2.63	0.000376	NHS Electronic Drug Tariff 2023
Phosphates enema (Formula B) 128 ml long tube	128	ml	41.32	0.322813	NICE British National Formulary (BNF) April 2023
Piperacillin 4 g/Tazobactam 500 mg powder for solution for infusion vials	45,000	mg	50	0.001111	NICE British National Formulary (BNF) April 2023
Prednisolone 5 mg/5 ml oral solution unit dose	50	mg	11.41	0.228200	NICE British National Formulary (BNF) April 2023
Propranolol 5 mg/5 ml oral solution sugar free	150	mg	27.69	0.184600	NICE British National Formulary (BNF) April 2023
Ranitidine	9750	mg	16.99	0.001743	NICE British National Formulary (BNF) April 2023
Rifadin 100 mg/5 ml syrup	2400	mg	4.27	0.001779	NICE British National Formulary (BNF) April 2023
Rifampicin 300 mg capsules	30,000	mg	144.26	0.004809	NICE British National Formulary (BNF) April 2023
Salbutamol 100 µg/dose inhaler	20,000	mg	6.3	0.000315	NICE British National Formulary (BNF) April 2023
Saline 0.9% nebuliser liquid 2.5 ml Steri-Neb unit dose	50	ml	6.53	0.130600	NICE British National Formulary (BNF) April 2023
Sanatogen A-Z Multivitamins and Minerals Tablets	30	Tablet	5.8	0.193333	NICE British National Formulary (BNF) April 2023
Senna 7.5 mg tablets 12 Years Plus	60	Tablet	1.49	0.024833	NICE British National Formulary (BNF) April 2023
Sildenafil 10 mg/ml oral suspension sugar free	1220	mg	186.75	0.153074	NICE British National Formulary (BNF) April 2023
Sodium bicarbonate 500 mg capsules	50,000	mg	18.75	0.000375	NICE British National Formulary (BNF) April 2023
Sodium chloride 292.5 mg/5 ml (1 mmol/ml) oral solution	100	ml	33.16	0.331600	NICE British National Formulary (BNF) April 2023
Sodium valproate 200 mg/5 ml oral solution sugar free	12,000	mg	7.56	0.000630	NICE British National Formulary (BNF) April 2023
Spironolactone	350	mg	21.1	0.060286	NICE British National Formulary (BNF) April 2023
Sytron oral solution	500	ml	14.95	0.029900	NICE British National Formulary (BNF) April 2023
Tacrolimus 0.1% ointment	30	g	14.38	0.479333	NICE British National Formulary (BNF) April 2023
Thiamine 100 mg/5 ml oral solution	2000	mg	23.97	0.011985	NICE British National Formulary (BNF) April 2023
Tramadol 10 mg/ml oral solution sugar free	1000	mg	4.5	0.004500	NICE British National Formulary (BNF) April 2023
Trihexyphenidyl 5 mg/5 ml oral solution	200	mg	105.28	0.526400	NICE British National Formulary (BNF) April 2023
Trimethoprim 50 mg/5 ml oral suspension sugar free	1000	mg	6.61	0.006610	NICE British National Formulary (BNF) April 2023
Trimethoprim tablets	1200	mg	0.5	0.000417	NICE British National Formulary (BNF) April 2023

Medication name	Quantity	Unit	Basic price (£)	Unit price (£)	Source
Valaciclovir 250 mg tablets	15,000	mg	123.28	0.008219	NICE British National Formulary (BNF) April 2023
Valaciclovir 500 mg tablets	5000	mg	12.25	0.002450	NICE British National Formulary (BNF) April 2023
Vitamin C 500 mg	15,000	mg	1.5	0.000100	Holland & Barrett
Warfarin 1 mg/ml oral suspension sugar free	150	mg	187	1.246667	NICE British National Formulary (BNF) April 2023
Xylometazoline hydrochloride 0.1% nasal spray	10	ml	2.65	0.265000	NICE British National Formulary (BNF) April 2023

Appendix 4 Annual % increases in previous year

Year	Price	Pay
2009–0	−1.30	1.80
2010–1	2.80	3.10
2011–2	4.10	0.90
2012–3	3.10	0.90
2013–4	1.80	0.70
2014–5	1.70	0.30
2015–6	0.45	0.30
2016–7	2.16	2.10
2017–8	1.07	1.22
2018–9	2.43	2.24
2019–20	1.62	2.53
2020–1	0.22	4.93

Appendix 5 Tables of illustrative quotes from qualitative interviews

Part 1: data extracts of acceptability of intervention to healthcare professionals

TABLE 45 Advantages of PCT test

Advantages of PCT test	Quote(s)
Combining PCT with other tools and increasing confidence	'Sometimes the more information you've got the easier it is to to make a a decision erm, that when you've kind of got a bit of information and perhaps its not totally clear. Erm, so I think it can just increase the confidence perhaps sometimes in the decision making erm and kind of add to that kind of the different things that you're looking because you're obviously looking at the patient and their you know all their observations. You're looking at how they are in themselves you know you're looking at all of the other blood results and erm things like that. So I think it just its just another part of the picture' (PID24)
PCT favourable to CRP, quicker decision, impact on patients and parents, and better hospital flow	'the children in whom I've used it the CRP has been coming down but probably not in the same league as the PCT so the PCT has dropped more rapidly which is reassuring and the CRP has lagged behind'... 'so it means that you can make a decision more quickly erm which is important in terms of parents, beds, you know flow in the hospital' (PID9) 'we're not opposed to it and if it was part of our test we would use it but but we're not gullible enough to feel it's it's the it's the be all and end all. It will be, my personal view is its like a CRP maybe a little bit better and tells you a bit more but it's not the make or break' (PID3)
PCT appears particularly useful for some patient groups, for example:	'where there's a question about whether its infection or non-infection that might be inflammation of *post-surgery*, after major surgery some of the other inflammatory markers we use are a bit more non-specific. The procalcitonin is probably most helpful in that distinction and that allows us to stop antibiotics or have more confidence when we're negotiating with other teams in trying to stop antibiotics when we have a low PCT so we can say well actually, you know, although you're worried that there was infection and you started antibiotics the procalcitonin's low, the CRP is often our other marker, that might be extremely high but there's no other evidence of infection, other tests are negative for infection so let's stop antibiotics' (PID25 interview 2)
Convince prescribers to stop antibiotics	'from doing antimicrobial stewardship round we would love to have the PCT, love to be able to do the PCT (hmm) because it's obviously it would give us back up to stop antibiotics sooner or at least switch to orals' (PID5)

TABLE 46 Disadvantages of PCT test

Disadvantages of PCT test	Quote(s)
Too much information is not helpful	'think you know the issue that its another test and its another thing to look at and although as I've just explained the benefits I think that that means you've got more information, sometimes too much information isn't helpful. Especially if lots of different things are saying slightly different, giving you a slightly different picture' (PID24)
Less faith in tests generally, CRP and PCT	'not understand the test, err not having faith that the test is erm worthwhile you know erm if they don't, as I said if they don't buy into that CRP is a useful test they potentially wouldn't for PCT either' (PID8)
PCT does not appears so useful for some patient groups, for example:	'there are some sort of specific pathologies, sometimes there's sort of abdominal collections where the procalcitonin doesn't appear to be quite as useful on occasion where all your other metrics are pointing at infection and yet your procalcitonin is extremely low and there are times when we've kind of had to go with our clinical judgment and sort of overrule the algorithm at that point when we don't feel comfortable stopping antibiotics because there are so many other clues or bits of information pointing at infection just the presence of the normal procalcitonin isn't enough to outweigh all of those other bits of information' (PID25 interview 2)
Cost	'the cost of it is perhaps another, I mean something you know its more costly than the CRP but if it changes, impacts on clinical decision making well then that cost is more than adequately reimbursed or whatever or recouped by better managing the patient so I don't think either of those in any way are insurmountable' (PID25)

TABLE 47 Barriers and facilitators to carrying out blood test in trial setting

Barriers and facilitators to carrying out blood test in trial setting	Quote(s)
Facilitator: PCT sample often taken with routine bloods	'no child that I was erm err providing clinical care for had err extra bloods taken. But I think that that that just represents the amount of blood tests that we do as part of routine care in PICU' (PID7 interview 2)
Facilitator: blood sample taken using IV line	'patients on intensive care they usually have erm so access that they can just take bloods without erm using like a finger prick or a needle so for those patients parents are usually absolutely fine of taking a sample whenever we want it erm and the nurses are very willing just to take a sample for us. But obviously we're not causing the child any distress because we're just taking it from a line that's already there' (PID26)
Facilitator: taking personal responsibility for running the test	'I didn't want to get too many people involved because then it's just open to error and obviously we usually only do get a small sample with it being babies so I don't want it wasted on someone's who's having a go and I want to make sure it's done properly' (PID20)
Facilitator: quick turna-round of test result for some	'we don't do it with routine labs we run the tests ourselves we've got a separate machine from ((COMPANY)) it means that you can, we can literally get the results in twenty minutes, half an hour which is amazing, rather than you know the number of times you're waiting for your CRP bloods and things to come back and you're calling the labs all the time going is it done yet, is it done yet and its quite nice that we have control over it and we can just do it' (PID11)
Barriers: slow turnaround of result for some	'that's the problem is it's mainly around the logistical organisation of the tests in a timely manner is the most important thing. We were told 9-5 but need to get it there by half 3' (PID17,18,19)
Barrier: difficulty getting value in dilutions	'only in some of the ones where we dilute, we don't get a value do we but that's just because once you dilute it you dilute whatever would have been there and so you just get an invalid result so that's been problematic some of the time' (PID20)

TABLE 48 Facilitators of algorithm

Facilitators of algorithm	Quote(s)
Straightforward	'very easily accessible and er very self-explanatory and erm yeah I think so far had good, very positive experience. There were issues to start with the algorithm so I think the current algorithm, the last version of it it's very easy to follow' (PID12 interview 2)
Seeing good outcomes	'they're generally happy to follow it and now we've been doing the study for so long and they've seen good outcomes where they've followed the algorithms I think they have a bit more confidence erm in following it' (PID11 interview 2)
Site Trial Team	'((Name)) done a really good job of going and meeting with those teams and discussing their concerns with them and I think it's probably helped some people erm so they're happy for us to approach all their patients and there's probably going to be some people who have been doing this a very long time and they've never going to change their ways now erm and there's probably not much you could do about it. But I think having that discussion and discussing their concerns with them erm seemed to have been quite effective here' (PID11 interview 2) 'having excellent research nurse definitely helps' (PID012 interview 1)
ID team	'the ones that erm where I have been involved erm I think you know I haven't found it difficult to use the algorithm within the study to help aid decision making, but we don't tend to do it in isolation either so because we've got an ID team in the hospital, erm they any child that's on antibiotics they have involvement with. So erm for the decision making regarding you know what we're going to do about the antibiotics using all available information and if a child's in BATCH using the PCT if they're in the intervention arm which would involve them as well in that discussion err in terms of you know decision making. So its not its not really left down to like an individual' (PID24)
Communication of result	'We would get those results phoned through to us by the IDs team or the microbiology team so actually they would have then interpreted the results and the clinical picture erm and err then provided us with advice at that point' (PID7 interview 2)

TABLE 48 Facilitators of algorithm (*continued*)

Facilitators of algorithm	Quote(s)
Algorithm reminder	'when it comes to the paediatric patients that our doctors see here that are on the PCT intervention arm I do try and explain the algorithm to them when I consent them so they know from the very beginning how the patients sitting at the start and where they go through the algorithm', 'plastered the doctor's office in the algorithm as well that they're consigned to' (PID23 interview 1)
AMS agenda	'I think in the Childrens' hospitals in UK there's a there is almost a dedicated workforce of infection specialists who spend a lot of time trying to use antimicrobials as sensibly as possible and that concept of stewardship I think the added value of procalcitonin to antimicrobial stewardship's team decision making is probably less than within other settings where you know antimicrobials are probably continued for longer and actually a nudge from a test like this will probably allow them to be switched and stopped in a more timely fashion. So personally, I think that procalcitonin will have maybe more of a role in a DGH setting or in a setting where you don't have a dedicated antimicrobial stewardship team who are making those decisions based on lots of other factors anyway' (PID25) 'we have a paediatric microbiology ward round and then its so very hot on antibiotics'…'we tend to not say oh we'll give them just 2 extra days just to make sure' (PID23)

TABLE 49 Barriers of algorithm

Barriers of algorithm	Quote(s)
Earlier version of algorithm was complicated	'it ((the algorithm)) was changed at the start it was visually incredibly complicated there was lots and lots of different boxes erm and just been streamlined now into the 2 lines of suspected or confirmed infection erm perhaps there could be a bit of a clarification about what a confirmed infections is because I sometimes have people who get confused and they say well we know they've got an infection but we don't know what the infection is, is that a confirmed or a not confirmed infection' (PID11 interview 2)
Mismatch with clinical picture	'if the clinical picture doesn't really fit erm the child's you know not going in the same direction of what you're seeing as a PCT result then that might make you decide not to follow the algorithm say for example the PCTs reduced to such that you could stop the course of antibiotics but actually the child themselves still remains quite unwell erm so that might then mean that you think well I'm not going to follow the algorithm because I'm going to treat the patient in front of me' (PID24) 'the algorithm at times felt very it felt quite conservative err and so I was involved in a few cases where the patient was much better, the procalcitonin had come down a lot but not enough according to the algorithm and so it seems a bit ridiculous to then insist on continuing the algorithm when the patient was obviously much better' (PID27)
Nervousness/anxiety when mismatch	'I recall some people getting a bit hung up on the algorithms and sort of getting, where maybe previously they would have just stopped the antibiotics sort of thing, anxious about the exact ins and outs of the algorithms' (PID27) 'generally good but now and then there's been scenarios where everybody is happy to stop but the PCT has still been very high and then it just creates a little bit of nervousness over what to do next' (PID 13, interview 2)
Risk–benefit, worst-case scenarios, and previous negative experiences	'certainly within microbiology and intensive care we maybe do look at these situations in very slightly different ways both understanding the thought processes, and the very valid points of each party's, but the microbiologist might be thinking far more around the sort of the stewardship and the, which is absolutely vital, erm as intensive care doctors certainly what I'm thinking is this kid is so sick erm any further deterioration is potentially going to be catastrophic for them erm and then it's a risk benefit analysis thing of and that process often leads to antibiotics being continued for longer than they maybe should be erm because we're looking after such a sick cohort of kids' (PID7) 'there may have been erm an incident or a or a tragedy that happened previously that they've put down to them not doing something or (yes yes) and therefor good luck shifting them away from that' (PID2)
Wariness	'I tend personally I I'm I don't blindly follow erm algorithms and protocols because maybe I'm just more erm what shall we say um cynical about this these things but but certainly in ICU we would certainly have more confidence in following its trend than CRP erm but it but we would still need to clinical backup to finally make so it's something that's not going to be used in isolation is it' (PID3)

continued

TABLE 49 Barriers of algorithm (*continued*)

Barriers of algorithm	Quote(s)
Lack of robust evidence	'I think we still don't really have a good handle on we don't have a good handle on other blood tests like CRP and how well they work. We have some really really bizarre results where the CRP is really low but the calcitonin's really high and then vice versa. So I think to be fair until actually the BATCH trial is completed its hard to really give its hard to give strong advice' (PID27) 'one of my big issues has been actually trying err get people to recognise that actually there is a lot of evidence behind the use of PCT, unfortunately most of it is from adult world' (PID8)
Children under care of other teams/specialties	'I've consented quite a lot of specialty children that come under things like orthopaedics and surgeons and they've not been all that great at following the algorithm because they're not paediatricians, erm so they tend to not want to tamper too much with antibiotics because they're not paediatric surgeons or paediatric erm arthropods so they're general surgeons, and they deal with adults the majority of the time' (PID23)
Not getting PCT result back in time for decision-making	'we've had a few where the CRP's come back, we haven't had a PCT at that morning ward round and they've made a decision before they've even seen the PCT' (PID 17,18,19)
Computer system	'PCT isn't one of those results that it would automatically pull through, so we could get it off the computer system but it wouldn't, you'd have to kind of you'd have to kind of go looking for it' (PID7 interview 2)
Forgetting or not understanding algorithm earlier in the trial	'when we first opened up, this is being very honest. The doctors didn't seem to sort of get get it' (PID 17,18,19) 'I think people got a bit more used to that idea as the trial went on' (PID28)

Part 2: data extracts of acceptability of intervention to parents

TABLE 50 Acceptability of intervention to parents

Acceptability of intervention to parents	Quote(s)
Concern over extra blood	'I was just like yes no I understand like that's fine whatever you do but just don't take any extra bloods and that was the only thing that I didn't want to have, I didn't want that extra like trauma for ((child))' (Parent PID 04)
Concern over deviation from usual practice	'I was just erm wanted to make sure that there was going to be no sort of massive deviation from ((name's)) care, that was, my only concern was ((name)) at that point in time so I think I just you know we had a little bit of a chat about it and I you know I just said I just need to make sure that he is he's not going to have a prolonged recovery through any sort of, you know if he was selected' (Parent PID 10)
Recall of intervention	Determine best antibiotic: 'well I think it was it was a he has infection we want it its got to go away yes and then it will be then it will be we're going to try and the thing that will basically we're going to take that test to determine what type of infection it is therefore we can determine what what's the best antibiotic to use' (Parent PID 15) Antibiotic review: 'said before that everything's come back fine you know quite well normal range blah blah blah we can reduce the amount of antibiotics that she's on based on that obviously as a parent you think yes she can come off the stronger doses' (Parent PID 03) Reassurance: 'so when it did come to be discharge time I remember the consultant coming to talk to ((child)) and saying you know we are, we are happy you know that you're well enough to go home and your most recent bloods the markers have decreased and he made a point of mentioning that actually the trial marker was also favourable and so I think that was an extra thing that reassured us' (Parent PID 09)

Part 3: data extracts of evaluation of trial processes

TABLE 51 Evaluation of trial processes

Evaluation of trial processes	Quote(s)
Parents reasons for taking part (or not)	Helping others: 'we would we would do it anyway if it helps other people. So we we straight away said we'd do it then and there because we don't need time to think about it' (Parent PID 05) Research needed for evidence based care: 'I think generally most people are keep to erm to help with research it's the only way that we get to you know prove the care we give and erm I think support it if we can and its ok for the individual erm then I think you know if we can can do these things I think its good' (Parent PID 14) Interest in antibiotic resistance: 'I'm a bit of a nerd on the news and the moment she said antibiotic resistance, I just said yes go for it because I know how important it is' (Parent PID 12)
The role of research nurses in communication and timing of approach	Timing was right: 'I thought it was fine I mean, for me obviously it was the ((day)) so she'd been in there you know a day and a night and that and erm obviously things were a lot more settled, she'd got through kind of the worse kind of initial shock about being in there and us panicking a bit we were more settled and you know I think it was quite good timing really' (Parent PID 06) Timing was too soon: 'a little bit as if it should have been left a little bit longer when he started to recover a little bit more it was a bit, I felt a bit bombarded'… 'we had so much going on and then as I say it was probably the next day we were there and we were still finding things out about what was going on with ((child))' (Parent PID 01) Specific 'window of time' to approach: 'possibly I felt like oh that's really quick however then obviously we're not we don't, there's no guarantee of how long we were going to be in there so I understand from another point of view a research point of view that that would erm I don't know from a, do you know I think it's alright I think like I think no I think it would be I think it was alright actually' (Parent PID 04) Time to read leaflet: 'bless them they ended up coming back a couple of times because I hadn't read it, it was just you know I put it in my bag and I just hadn't read it, because then I started work and then didn't you know it was just, I'm doing everything else but, but then I did read it erm but they did come back a couple of times. They weren't you know persistent or anything like that but they were just giving me the time, to acknowledge it and to take it in' (Parent PID 07)
Trial materials	*Leaflet/PIS* 'I didn't have any problems with it at all, very very it was thorough, and it was erm concise' (PID Parent PID 07) 'his questions were things like, are there any risks involved, could she get an infection from from it you know someone taking the blood you know between me and the nurses explaining bloods you know theres a very low chance of getting infections from taking bloods because they sterilise the area and all that erm but I don't know if that was actually written in … you know that theres no risks involved' (Parent PID 03) *Consent form* 'I can't think of anything of the top of my head I just remember thinking it's a good idea and signing it' (Parent PID 12) '…in the end, I just signed it because I just wanted it done and out the way really (laughs)' (Parent PID 01)
Contamination and usual behaviour	'I don't think that's probably, nothing's really changed in terms of routine care yet' (PID11 interview 1) 'it's starting to become more available, in our intensive care they're ordering it clinically. Erm starting to become more frequent erm and there's been a couple of occasions where they've ordered a PCT test and they've been in a control arm and then ((name of PI)) has generally spoken to them and said you know we're in the study we shouldn't be doing this they're the control arm we want to make sure that it's you know they're only getting the PCT test if they're in the PCT arm' (PID11 interview 2) *Impact of COVID* 'it wasn't possible before the study was conducted. There have been one or two in children in whom, one thing that COVID has done is that procalcitonins were used extensively on adults during the COVID pandemic especially on adult ITU. So, there's perhaps one or two children in the past 12 months who have had a procalcitonin who have been linked to intensive care settings' (PID25 interview 2)
Randomisation and equipoise	*Parental preference for trial arm* 'I mean I would have liked him to be in the new one only because I think that that's where you know a lot of the research will be erm but no other than that no it was fine' (Parent PID 07) 'happy to be either if its something that's going to help sort of you know future research' (Parent PID 11) *HCP equipoise* 'every bit of information is useful or you know is useful so having the PCT is useful so then the ones that aren't on that arm er kind of feel like there's a little bit of information missing' (PID 13 interview 1) 'it definitely changed my practice so erm if we have got PCT results, it helps me to er decide whether to stop or switch or to continue on antibiotics. And I know my colleagues in ICU they had very positive experience and erm quite often they ask now sort of you know can we enrol this patient in to the BATCH trial so they can check PCT' (PID12 interview 1)

EME
HSDR
HTA
PGfAR
PHR

Part of the NIHR Journals Library
www.journalslibrary.nihr.ac.uk

Published by the NIHR Journals Library