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Applying clinical decision aids for the assessment and management of febrile infants presenting to emergency care in the UK and Ireland: Febrile Infant Diagnostic Assessment and Outcome (FIDO) Study protocol

Etimbuk Umana ,[1] Clare Mills,[1] Hannah Norman-Bruce ,[1] Kathryn Wilson,[1] Hannah Mitchell,[2] Lisa McFetridge,[2] Kerry Woolfall,[3] Fiona A Lynn ,[4] Gareth McKeeman,[5] Steven Foster,[6] Michael Barrett ,[7,8] Damian Roland,[9,10] Mark D Lyttle ,[11,12] Chris Watson,[1] Thomas Waterfield[1,13]

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For numbered affiliations see end of article.

Correspondence to
Dr Etimbuk Umana;
Eumana01@qub.ac.uk

ABSTRACT

Introduction Febrile infants 90 days and younger are at risk of invasive bacterial infections (bacteraemia and meningitis) and urinary tract infections. Together this is previously termed serious bacterial infection with an incidence of approximately 10–20%. The National Institute for Health and Care Excellence guidance advocates a cautious approach with most infants requiring septic screening, parenteral broad-spectrum antibiotics and hospital admission. Internationally, variations exist in the approach to febrile infants, with European and North American guidance advocating a tailored approach based on clinical features and biomarker testing. None of the available international clinical decision aids (CDAs) has been validated in the UK and Irish cohorts. The aim of the Febrile Infant Diagnostic Assessment and Outcome (FIDO) Study is to prospectively validate a range of CDAs in a UK and Irish population including CDAs that use procalcitonin testing.

Methods and analysis The FIDO Study is a prospective multicentre mixed-methods cohort study conducted in UK and Irish hospitals. All infants aged 90 days and younger presenting with fever or history of fever (≥38°C) are eligible for inclusion. Infants will receive standard emergency clinical care without delay. Clinical data and blood samples will be collected, and consent will be obtained at the earliest appropriate opportunity using research without prior consent methodology. The performance and cost-effectiveness of CDAs will be assessed. An embedded qualitative study will explore clinician and caregiver views on different approaches to care and perceptions of risk.

Ethics and dissemination This study was reviewed and approved by the Office for Research Ethics Committees Northern Ireland-Health and Social Care Research Ethics Committee B, Public Benefit and Privacy Panel for Health and Social Care Scotland, and Children's Health Ireland Research and Ethics Committee Ireland. The results of this study will be presented at academic conferences and in peer-reviewed publications.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first prospective multicentre study in the UK and Ireland looking at the management of febrile infants 90 days and younger.
⇒ There is a good geographical spread of both urban and regional sites undertaking this study.
⇒ Using qualitative interviews with parents and clinicians, we will be able to gain in-depth insight on how risk is communicated and managed in febrile infants.
⇒ Research without prior consent methodology will be used to enable pragmatic recruitment of infants in the acute setting and appropriate follow-up consent procedure undertaken.
⇒ Due to study samples being obtained only during the first episode of phlebotomy, an estimated 400 or more samples are likely to be obtained for biomarker analysis.

Trial registration number NCT05259683.

INTRODUCTION

Febrile infants under 90 days of age are at a higher risk of invasive bacterial infections (IBIs) and urinary tract infections (UTIs) than older children. Several studies have reported the rate of IBI in this cohort to be around 3%, whereas UTI rates can range from 9% to 17%.[1–5] Unlike older children, infants regularly appear well or have non-specific features despite having IBI or UTI (previously collectively termed serious bacterial infection (SBI)).[3 6–9] For these reasons, most clinical decision aids (CDAs) advise a

low threshold for parenteral antibiotics, lumbar puncture (LP) and admission to hospital.[3 4 6 7]

In the UK, the National Institute for Health and Care Excellence (NICE) CDA NG51 'Sepsis: recognition, diagnosis and early management' recommends that all febrile infants under 3 months old receive parenteral antibiotics as soon as possible, irrespective of age, clinical appearance or laboratory results.[8] In contrast, NICE NG143 'Fever in under 5s: assessment and initial management' and the British Society for Antimicrobial Chemotherapy (BSAC) CDAs advise tailored approaches based on age, clinical assessment and laboratory testing including C reactive protein (CRP).[9 10] These CDAs have been validated in the UK and Ireland using retrospective data from six sites (n=555).[5] The NICE and BSAC CDAs advised that 85–100% of included infants should receive parenteral antibiotics despite only 2% having an IBI.[5]

Internationally, approaches vary and many CDAs from mainland Europe and North America advocate a tailored approach to the management of febrile infants, obviating the need for LP, antibiotics and admission in low-risk groups.[3 4 6] These CDAs include StepByStep, Pediatric Emergency Care Applied Research Network (PECARN) and Aronson CDAs. In contrast to the NICE and BSAC CDAs, StepByStep and PECARN CDAs require procalcitonin (PCT) testing rather than CRP testing. Only one CDA currently exists that allows for the use of either CRP or PCT interchangeably in the assessment of febrile infants.[7] The American Academy of Pediatrics (AAP) CDA published in 2021 advises tailored care based on age, clinical appearance, laboratory results, and CRP or PCT results.[7] These international CDAs have been validated in a range of settings across Europe and North America with reports that 45–54% of infants can be safely discharged without parenteral antibiotics depending on the CDA and cohort.[3 4 6 11] None of the international CDAs requiring PCT have been assessed in UK cohorts.

OBJECTIVES

The aim of the Febrile Infant Diagnostic Assessment and Outcome (FIDO) Study is to prospectively validate a range of CDAs in the UK and Irish populations, including CDAs that use PCT testing.

Primary objectives

- Report the aetiology of IBI and UTI (previously known as SBI) in febrile infants 90 days of age and under in the UK and Ireland.
- Describe the clinical and laboratory predictors of IBI and UTI in febrile infants 90 days of age and under.
- Report the performance of tailored CDAs to correctly identify a cohort suitable for management without parenteral antibiotics.
- Report the performance of tailored CDAs to correctly identify a cohort suitable for management without LP.

Secondary objectives

- Report on the cost-effectiveness of alternative CDAs.
- Report parents/guardians' and clinicians' views on how best to communicate different treatment strategies, including the risks and benefits of each strategy.

METHODS

This protocol adheres to the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis; Standards for Reporting of Diagnostic Accuracy criteria; and Consolidated Health Economic Evaluation Reporting Standards statement.[12–14]

Study design

A prospective mixed-methods multicentre observational cohort study conducted in the UK and Ireland. Thirty-five Paediatric Emergency Research in the UK and Ireland (PERUKI) sites are currently participating in the FIDO Study from 6 July 2022 to 31 August 2023.

Study population

All infants 90 days of age and under with a fever of ≥38°C during their time in the emergency department (ED) or assessment unit (AU) or with a history of fever of ≥38°C recorded by anyone via any thermometer type within the last 24 hours of presentation. Infants will be excluded if consent is declined or withdrawn from the study and if the parent/guardian is unable to consent.

Screening

Potentially eligible participants will be screened by appropriately trained clinical and research staff using a case report form (CRF). This will take place in UK and Irish EDs and AUs.

Procedure

All eligible participants will be enrolled and, in all instances, routine care will not be interrupted or delayed. During emergency care, CRF1 will be completed contemporaneously by the clinical staff or local study teams. CRF1 records non-personal data, such as baseline demographic data, clinical features and initial examination findings. The CRF1 data include all clinical data susceptible to recall bias. Seven days after discharge, CRF2 will be retrospectively completed by a trained member of the local study team. CRF2 includes data that are less susceptible to bias, such as length of stay, treatments given, laboratory results and any subsequent unplanned reattendances. Where possible, additional blood will be collected and stored as plasma for PCT testing. The flow diagram of the study procedure is shown in figure 1.

Blood plasma collection and storage

During routine phlebotomy, up to 1 mL of additional blood will be collected, no additional phlebotomy events will be performed beyond those required for usual care. The blood taken during routine phlebotomy will be collected for PCT testing and stored for subsequent biomarker discovery and validation. If insufficient blood

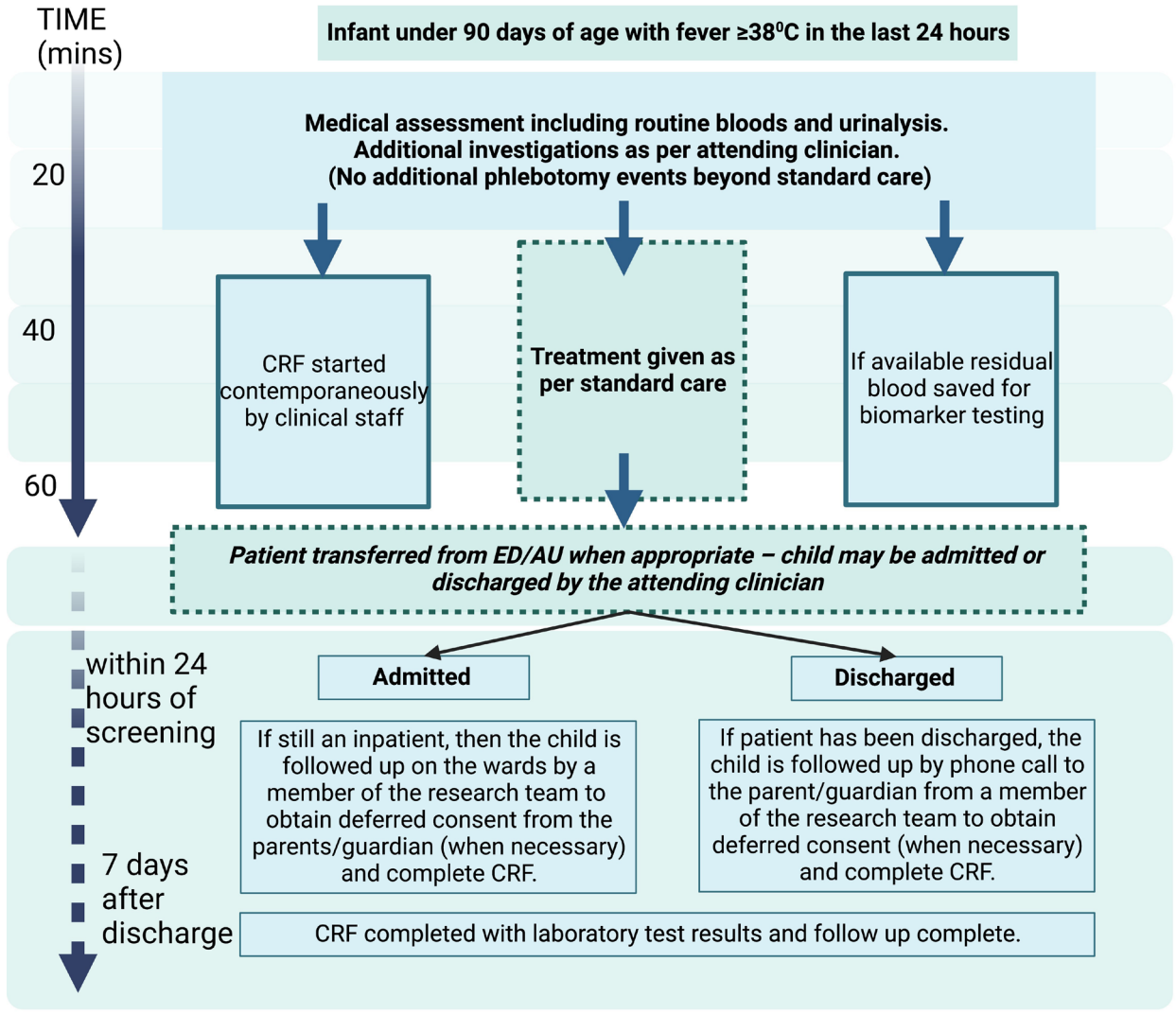

Figure 1 Flow diagram of study procedure. AU, assessment unit; CRF, case report form; ED, emergency department.

is available, then routine testing will be prioritised. Blood samples will be collected in EDTA plastic vacutainers, processed and stored locally as frozen plasma. The standard operating procedure for sample processing and storage can be found in the online supplemental appendix 1. Frozen study samples will be transferred to a central laboratory at Queen's University Belfast and will undergo PCT testing at the Department of Clinical Biochemistry Laboratory, Royal Victoria Hospital Belfast. The Elecsys BRAHMS PCT assay on the Roche e801 will be used for analysis of plasma samples. Staff at the Royal Victoria Hospital laboratory are blinded to all study clinical data and reference standards. Table 1 provides the timeline for study assessment.

Definitions

The diagnosis of IBI, including meningitis, bacteraemia and UTI (excluding contaminants), is described below.

Table 1 Study assessments

		Follow-up	
	At presentation	0–24 hours	7 days after discharge
Screening and data entry CRF	X		
Initial blood sample obtained and stored within 24 hours	X	X	
Consent discussion		X	
Notes review and CRF checking by member of research team		X	
Notes review and CRF completion by member of research team			X

CRF, case report form.

Urinary tract infection

UTI will be confirmed by >100 000 CFU/mL of a single organism from a single clean urine (clean catch, suprapubic aspiration, urethral catheter specimen) or >100 000 CFU/mL of the same single organism from two non-clean urines (pads, bags, cotton wool) and the presence of pyuria (>5 white blood cells per high-power field) on laboratory microscopy.

Meningitis

Meningitis will be confirmed by culture or molecular testing of cerebrospinal fluid using United Kingdom Accreditation Service (UKAS) accredited National Health Service (NHS) laboratories. The reference standard test will be performed by staff blinded to the clinical data and the suspected diagnosis.

Bacteraemia

Bacteraemia will be confirmed by culture or molecular testing of blood using UKAS-accredited NHS laboratories. The reference standard test will be performed by staff blinded to the clinical data and the suspected diagnosis.

Contaminants

Contaminants include coagulase-negative *Staphylococcus*, *Propionibacterium acnes*, *Streptococcus viridans* or diphtheroids. A list of all suspected contaminants will be provided at the end of the study.

Outcome measures

Primary:

1. IBI.
2. UTI.

Secondary:

1. Length of stay.
2. Hospital admission.
3. Parenteral antibiotic usage.
4. Procedures performed.
5. Unplanned reattendance within 7 days.

Data handling

The only people with access to personal data (other than the clinical team caring for the child) will be the principal investigator and nominated site research team at the participating sites. These individuals will have received study-specific training and completed their Good Clinical Practice (GCP) training. Clinical data and outcomes will be recorded on the CRF. The CRF and linkage logs will be stored in a predesignated office cabinet which is under lock and key, along with either lock access or security card access to the stored room. Data will be pseudoanonymised at site. Pseudoanonymisation will be necessary at site level to enable data queries and audit research purposes. The CRF will be uploaded to the Research Electronic Data Capture (REDCap) at the Queen's University Belfast servers and made available for further research. REDCap is a secure web application for building and managing online surveys and databases. REDCap is compliant with the GCP and the European General Data Protection Regulation on data management.[15 16] Sites will have the option to either use the electronic CRF (REDCap) or use paper forms and then upload the CRF to the REDCap server. This will depend on site infrastructure and research capacity. All data uploaded to the REDCap database will be non-personal data.

Consent

Febrile infants are at high risk of IBI and UTI. Their initial assessment and management is a medical emergency. Therefore, it is not possible or appropriate to discuss research during the initial assessment and resuscitation phases. For this study, we will use research without prior consent (RWPC) methodology.[17 18] This approach has been shown to be effective and acceptable to both parents and clinicians for diagnostic studies based on prior works such as the Petechiae in Children Study.[19 20] RWPC has also been used in the EcLiPSE trial undertaken by PERUKI.[21] In all instances, consent to include data and blood plasma in the study will be sought at the earliest appropriate opportunity. No research sample will be transferred out from the local hospital without prior consent obtained. If consent is declined, then the blood plasma sample and all data will be excluded from the study. A list of non-consenting participants will be compiled.

Face-to-face consent discussion

A trained member of the research team will be notified of enrolment at the earliest appropriate opportunity (ideally less than 24 hours after admission/attendance). The research team member will then liaise with the clinical team to ascertain the condition of the child and parents, and determine the appropriateness of seeking consent at that time. In the majority of cases, a consent discussion will take place within 24 hours of admission/attendance. In circumstances where the child is too unstable or an approach is deemed inappropriate by the clinical team, then discussions will be delayed until a more appropriate time.

Virtual consent discussion

Some participants will be discharged before face-to-face consent discussions can occur. In this instance, the research team will contact the parents/guardians by telephone/videoconferencing facility and explain the study and the RWPC process. The researcher will seek verbal consent and provide pack 1 (consent letter 1, participant information and consent form) by post/email. If after 4 weeks there is no response, pack 2 (consent letter 2, participant information sheet and consent form) will be sent in the post/email. If no reply is received after 4 weeks, the blood plasma sample will be excluded from the study and anonymised clinical data will be included in the study.

Death prior to consent

This is likely to be a rare occurrence but almost certainly could occur. When a participant dies before consent has

been sought, the site principal investigator or nominated deputy will obtain information from clinical colleagues and establish the most appropriate practitioner to notify parents of research involvement. Consent can be sought from parents/guardians following the death of their child and prior to the parent's departure from the hospital. However, it is at the discretion of the clinical staff to determine whether it is appropriate for each individual family. It may be that it is not appropriate for consent to be obtained prior to discharge. Following the death of a child, it is common practice to invite parents/guardians to a meeting with the consultant in charge of their child's care after death. This usually takes place days or weeks after death. At this meeting, the consultant will be asked to explain the study, reasons for research without prior consent, how to opt in or out of the study, and provide contact details if the parents/guardians wish to discuss the study with a member of the research team (either in person or by telephone). Following the meeting, a personalised letter/email (bereaved letter 1), including the participant information sheet and consent form, will be sent to the bereaved family (bereaved pack 1). This letter will explain the study, reasons for RWPC, how to opt in or out of the study, and provide contact details if parents wish to discuss the study with a member of the research team (either in person or via telephone). If after another 4 weeks after sending the initial letter/email to the bereaved family, there is no response, a follow-up letter/email (bereaved letter 2) along with the participant information sheet and consent form will be sent to the bereaved family (bereaved pack 2). This second letter will explain the study, reasons for RWPC, how to opt in or out of the study, and provide contact details if parents wish to discuss the study with a member of the research team (either in person or via telephone). In addition, this letter/email will also confirm that if no consent form is received within 4 weeks of the letter being sent, then only the participant's anonymised data will be included in the study, and any stored blood plasma will be excluded from the study and destroyed. This approach is based on CONsent methods in childreN's emergEncy medicine and urgent Care Trials (CONNECT) guidance for conducting RWPC in children.[17] The CONNECT guidance is an evidence-based guideline for the use of RWPC in children.

Withdrawal of consent

The parent/guardian is free to withdraw consent to participate in the study at any time, without providing a reason. Their withdrawal will have no bearing or implication on the clinical care their child receives. The study team will maintain a record of all those who withdraw consent to participate in the study.

Risks and benefits

There are no benefits from taking part in this study. All participants receive usual care without delay, as per local guidance, and there are no additional procedures. All personal data will be stored on-site by the principal investigator and only routinely collected, non-personal pseudonymised clinical data will be uploaded to the REDCap database.

Sample size justification

From pilot retrospective work in six sites similar to those that will be participating in the study, 555 patients had full data from over 1300 screened for eligibility.[5] This pilot study was conducted over a 12-month period and recruitment ranged from 45 to 151 participants per site.[5] We aim to recruit 1000 from over 30 PERUKI sites. It is anticipated that in 12 months, it will be possible to screen 2000 febrile infants with over 400 stored plasma samples for biomarker analysis.

Statistical analysis plan

The demographic characteristics, vaccination status, risk factors, reported symptoms, clinical assessment, parenteral antibiotic use, admission to hospital, viral testing, admission to intensive care units and survival of the FIDO Study population will be presented as descriptive statistics. The mean (SD)/median (IQR) will be used for continuous covariates, and the frequency and percentages for binary and categorical covariates. The performance of the CDAs and clinician performance will be compared by calculating the sensitivity, specificity, negative predictive values and positive predictive values (with 95% CIs). The McNemar's test will be used to assess differences in sensitivity and specificity between the CDAs and clinician practice.

A stepwise approach to assess clinical risk factors will be used. Initially, all possible predictors will be assessed by univariate analysis with χ^2 testing of categorical data and with the Mann-Whitney U test for continuous data. Age-dependent predictors, such as heart rate, respiratory rate and blood pressure, will be converted to categorical data and classified within or outside published normal ranges. All predictors showing a significant association with IBI and UTI (ie, with a p value of <0.20) will be included in a binary multivariable logistic regression model. A liberal level of significance ($p<0.20$) will be used to avoid falsely excluding a significant variable based on univariate analysis alone. The predictors identified from the univariate analysis will then be included in logistic regression modelling. Empirical binary multivariable forward and backward logistic regression modelling will be used to identify a best-fit model to distinguish children at the highest risk of SBI. Multiple imputation will be undertaken to impute missing data. Analysis will be repeated with imputed data and with incomplete data sets excluded. Sensitivity analysis for the validation of CDAs will be performed for the following subgroups: age, fever without a source, comorbidities and different biomarker thresholds.

Health economic evaluation

A cost-effectiveness analysis (CEA) will be conducted alongside the cohort study, estimating the incremental

cost per additional false-positive result averted. A decision analytical model will be constructed to compare the cost-effectiveness of each alternative CDA with usual care, following guidelines on good practice.[22] The CEA will take the provider (UK NHS) perspective, as recommended by NICE.[23] The time horizon for the decision analytical model will reflect the cohort study from attendance at ED/AU to 7 days after discharge. Estimates of effect will be derived from findings on sensitivity and specificity of the diagnostic testing procedure advocated by each CDA. Estimates of costs will take a bottom-up, micro-costing approach. Healthcare service resource use for each participant will be measured using data collated for the CRF and sourced from routine data. These activities of resource use will be costed in UK sterling at 2021/2022 prices using published UK national unit costs.[24] Activities not covered by these sources will be valued at market prices. The average cost per patient to the UK NHS will be estimated. Model parameters will be obtained from the cohort study or best available evidence, sourced from a targeted search of the literature, and discussed with experts where model assumptions are required. Incremental cost-effectiveness ratios (ICERs) will be presented for each alternative CDA compared with usual care in terms of the incremental cost per additional false-positive result averted. Guidance on characterising model uncertainty[25] will be followed. Uncertainty in estimates of costs, effects and net benefit will be presented through bootstrapped 95% CIs using 10 000 iterations to replicate a larger cohort. This probabilistic sensitivity analysis will be carried out with probability distributions applied to key model parameters to provide a correct estimate of expected effects, costs and net benefit and test whether the ICERs are sensitive to change. Assessment of heterogeneity in cost-effectiveness[26] will be performed, if feasible, for different types of patients. These subgroups will include infant age (<28 days vs ≥28 days), clinical appearance (well looking vs ill looking) and infant risk status, as categorised by the relevant CDA (low vs high risk).

Embedded qualitative study

This embedded study aims to explore how clinicians and parents understand, balance and communicate risk when making decisions regarding different treatment strategies for febrile infants.

Interviews will explore parents' experiences of emergency care and understand how clinicians structured their conversations around the risks and benefits of different treatment strategies and parents' views on how such information should be discussed in future clinical care. Clinicians' risk tolerance will also be assessed when examining the implementation of different CDAs. This embedded qualitative study will be undertaken by KWi and KWo. The findings will be used to understand which of the different treatment strategies is most acceptable to parents and guardians and to develop a framework for structuring future clinical conversations, including how to communicate the risks and benefits of different treatment strategies.

Recruitment and consent for interviews

A member of the research team will ask the parent/guardian to read the relevant section of the participant information sheet and provide contact details on the consent form if they wish to participate in an interview via face-to-face, telephone or online platforms (eg, Microsoft Teams). Parents and legal guardians who decline consent for other aspects of the FIDO Study can still consent to participate in an interview. Those who consent to the interview will be contacted and invited to participate in an interview at a later date (within 6 weeks).

Clinicians who register an interest in taking part in an interview will be sent a copy of the practitioner information sheet and consent form, which they will be asked to read, sign and return prior to the interview. Interviews will take place face-to-face, online (eg, Microsoft Teams) or via telephone. Participants will receive a small voucher payment to thank them for their time.

Sampling

Based on previous research in this area, we anticipate interviewing approximately 15 parents/guardians. A further 5–10 clinicians will be invited for an interview. Sample size will be determined by the concept of information power, which considers factors such as the aims of the study, sample specificity (to include mothers, fathers and clinicians from a range of sites) and quality of dialogue to guide how many interviews to conduct.[27] Participants who have agreed/consented to participate in the qualitative interview will have information logged on the data linkage log by site research team. The only data transferred to the interviewers for the qualitative interview will be names and contact details to arrange interviews.

Interview conduct

All interviews will be conducted by a trained member of the research team (KWi). Topic guides for both patients/guardians and clinicians will be developed using previous literature. Respondent validation will be used so that previously unanticipated topics will be added to the topic guides and discussed with participants as further interviewing and analyses progress.

Any distress during the interviews will be managed with care and compassion, as per the distress protocol, and participants will be free to decline to answer any questions that they do not wish to answer or to stop the interviews at any point. Any such individual will be supported in obtaining appropriate help, and where appropriate, the lead clinician responsible for the child's care will be informed to offer any support.

Analysis

Qualitative interview data will be transcribed, checked and anonymised as the study progresses. QSR NVivo software will be used to assist in the organisation and

indexing of qualitative data. Data will be analysed thematically,[28] while the analysis will be informed by the constant comparison approach of grounded theory.[29] The focus will be modified to fit with the criterion of catalytical validity, whereby findings should be relevant to future research and practice.

Patient and public involvement

A patient and public involvement (PPI) advisory group was consulted for the FIDO Study. The advisory group supported the objectives and process of the study protocol and agree with the RWPC approach suggested. The PPI group provided feedback on project design, the use of RWPC and patient-facing documents.

Ethics and dissemination

This study has been reviewed and given approval by the Office for Research Ethics Committees Northern Ireland-Health and Social Care Research Ethics Committee B, Public Benefit and Privacy Panel for Health and Social Care Scotland, and Children's Health Ireland Research and Ethics Committee Ireland. This study is conducted in accordance with the guidelines of the Declaration of Helsinki and GCP. The FIDO Study has been registered on https://clinicaltrials.gov/ (NCT05259683). Data from the FIDO Study will be presented at internal and external educational/academic meetings and in publications in high-impact medical journals. In all presentations and publications, only non-identifiable pooled results will be presented. We hope that this information will inform practice and guideline development.

DISCUSSION

There is a current move towards tailored care for febrile infants internationally[3 4 7]; however, in the UK and Ireland, febrile infants are managed conservatively.[8] The impact of conservative management, which includes invasive investigation (blood and LP), antibiotic therapy and hospital admission, leads to downstream effects in these infants, particularly if they are at low risk of IBI and UTI.[30]

The FIDO Study is a multicentre prospective study and is being conducted across a range of hospital settings in the UK and Ireland. This study aims to generate a large prospective data set to help answer relevant questions regarding the management of febrile infants with a focus on UK and Irish practices. Understanding the application of various CDAs and their associated costs will help guide clinicians in the best approach for managing these infants, in particular, the impact of applying these CDAs to determine a low-risk population who can be safely discharged or have invasive testing averted. For CDAs using PCT,[3 4 7] this could be an additional cost when incorporated into current practice. Therefore, validation of CDAs, such as the AAP CDAs[7] where CRP could be substituted for PCT, is important as well as comparing the diagnostic accuracy of both biomarkers. The qualitative study examining the communication of the risks and benefits of various approaches between clinicians and parents will help build a conceptual framework and identify commonalities to improve the understanding and communication for both groups. Through this qualitative study, clinicians' risk tolerance will also be assessed, an area highlighted by the AAP CDA.[7] Challenges exist with the delivery of a study of this scale, including winter pressures on EDs, workforce and staffing issues. Making recruitment pragmatic and using the RWPC will enable stable and progressive recruitment during this period.

This study has some limitations. One main limitation is that not all infants have plasma stored for PCT and future biomarker analysis. This is due to the difficulty in obtaining additional samples in this cohort while prioritising emergency care. Follow-up will only be performed for 7 days post-discharge. One of the aims of this study is to collect data on all acute presentations related to the first initial presentation. Our inclusion criteria are broad compared with other studies.[3 4] However, the aim is to get a representative sample of infants to report the epidemiology of IBI and UTI in this cohort. We have also moved away from the term SBI because of the heterogeneity observed in prior studies in terms of the infections included. Based on the AAP recommendations, we decided to focus on IBI and UTI as outcomes.[7]

Author affiliations
[1]Wellcome Wolfson Institute For Experimental Medicine, Queen's University Belfast, Belfast, UK
[2]Mathematical Sciences Research Centre, School of Mathematics & Physics, Queen's University Belfast, Belfast, UK
[3]Department of Public Health, Policy and Systems, Faculty of Health and Life Sciences, Institute of Population Health, University of Liverpool, Liverpool, UK
[4]School of Nursing and Midwifery, Queen's University Belfast, Belfast, UK
[5]Department of Clinical Biochemistry, HCS Belfast Health and Social Care Trust, Belfast, UK
[6]Emergency Department, Royal Hospital for Children, Glasgow, UK
[7]Paediatric Emergency Medicine, Children's Health Ireland at Crumlin, Crumlin, Ireland
[8]Women's and Children's Health, School of Medicine, University College Dublin, Dublin, Ireland
[9]Emergency Department, Paediatric Emergency Medicine Leicester Academic (PEMLA) Group, Leicester, UK
[10]Department of Health Sciences, University of Leicester, Leicester, UK
[11]Emergency Department, Bristol Royal Hospital for Children, Bristol, UK
[12]Faculty of Health and Applied Science, University of the West of England, Bristol, UK
[13]Emergency Department, Royal Belfast Hospital for Sick Children, Belfast, UK

Twitter Etimbuk Umana @timburgD, Michael Barrett @DrMBarrett, Damian Roland @damian_roland and Mark D Lyttle @mdlyttle

Collaborators On behalf of Paediatric Emergency Research in the UK and Ireland (PERUKI).

Contributors EU, CM, HM, LM, KWo, FAL, DR, MDL, CW and TW were involved in the conception and design of this protocol with input from HN-B, SF, KWi, GM and MB. TW is the chief investigator and EU is the researcher. EU, CM, GM, CW and TW designed sample collection, storage and analysis. EU, KWo, KWi and TW developed the section for the qualitative interviews. EU, FAL and TW conceptualised the design for the economic analysis evaluation. HM, LM and EU will oversee the statistical analysis. EU wrote the first draft of the manuscript. All authors read, critically revised and approved the final version of the manuscript.

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ORCID iDs
Etimbuk Umana http://orcid.org/0000-0002-0780-8614
Hannah Norman-Bruce http://orcid.org/0000-0002-0792-5490
Fiona A Lynn http://orcid.org/0000-0002-0216-643X
Michael Barrett http://orcid.org/0000-0003-1775-8347
Mark D Lyttle http://orcid.org/0000-0002-8634-7210

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