**Title:**

Validating clinical decision aids for the assessment and management of febrile infants presenting to emergency care in the UK and Ireland.

**Short Title**

Febrile Infant Diagnostic Assessment and Outcome (FIDO) Study

**Protocol**

**Version: 3**

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# Glossary

|  |  |
| --- | --- |
| BSAC | British Society for Antimicrobial Chemotherapy |
| CDA | Clinical Decision Aids |
| CRF | Case Report Form |
| CRP | C-Reactive Protein |
| CSF | Cerebrospinal Fluid |
| DGH | District General Hospital |
| IBI | Invasive Bacterial Infection |
| NICE | National Institute for Health and Care Excellence |
| NHS | National Health Service |
| POC | Point-of-care |
| PICU | Paediatric Intensive Care Unit |
| PCR | Polymerase Chain Reaction |
| PCT | Procalcitonin |
| RWPC | Research Without Prior Consent |
| SBI | Serious Bacterial Infection |
| UTI | Urinary Tract Infection |

# Protocol Summary

|  |  |
| --- | --- |
| **Full title:****Short title:****Rationale:** | Validating clinical decision aids (CDAs) for the assessment and management of febrile infants presenting to emergency care in the UK and Ireland. Febrile Infant Diagnostic Assessment and Outcome (FIDO) StudyFebrile infants under 3 months of age represent a high risk group for serious bacterial infection (SBI) with approximately 10-20% having bacteremia, meningitis or urinary tract infection. The assessment of febrile infants is challenging, and current National Institute for Health and Care Excellence (NICE) guidance advocates a cautious approach with the majority of infants requiring a septic screen, parenteral broad-spectrum antibiotics, and admission to hospital. Internationally there is significant variation in the approach to febrile infants with European and USA guidance advocating a tailored approach based on clinical features and biomarker testing. None of the available clinical decision (CDAs) have been validated in a UK and Irish cohort.  |
| **Study type:** | Prospective cohort study |
| **Population:** | Infants under 90 days of age with a measured fever ≥38oC within 24 hours of presentation. |
| **Sample size****Study sites:** | A convenience sample of approximately 2000 infantsApproximately up to 30 PERUKI Sites |
| **Study duration:****Interventions:****Outcome measures:** | 12 months Symptoms, clinical features and laboratory results recorded on an electronic case report form (CRF) by the attending clinician. Where possible 1ml of blood plasma will be collected, during routine phlebotomy, and stored for additional biomarker discovery and validation. * Performance accuracy of CDAs
* Cost analysis of different approaches
* Aetiology of febrile illnesses in young infants
 |

# Background

Infants below three months of age are at high risk of serious bacterial infections (SBI) including urinary tract infections (UTI), bacteremia and meningitis (1–4). Recent studies have reported the rate of SBI in the range of 10 – 20% , while invasive bacterial infection (IBI) such as bacteremia and meningitis to be up to 3% (1–5). Unlike older children infants regularly appear well or have non-specific features despite having a SBI, with history and physical examination alone not sufficient to detect all cases of SBI (3,6–9). Furthermore, the clinical differentiation between fever caused by bacteria and viruses is most challenging in the less than three-month age group. The majority of children still have self-limiting illness in this age group making risk assessment challenging for clinicians.

The ideal approach to the assessment and management of febrile infants is not clear, as exemplified by the contrasting approaches advocated by the National Institute for Health and Care Excellence (NICE). The NICE guideline NG51 “Sepsis: recognition, diagnosis and early management” advises that all febrile infants (under 3 months of age) receive parenteral antibiotics immediately whereas NICE guideline NG143 “Fever in under 5s: assessment and initial management” suggests a tailored approach based on clinical assessment and laboratory testing (10,11). The recently proposed British Society for Antimicrobial Chemotherapy (BSAC) guidance also supports a tailored approach similar to the NICE guideline NG143 (12). These clinical decision aids (CDAs) were recently validated through the Paediatric Emergency Research UK and Ireland (PERUKI) network (5). They all (NICE NG51, NG143 and BSACS) had high sensitivity but poor specificity with none of the CDAs able to identify reliably a low risk population (see table 1)(5).

Internationally several other CDAs exist including Boston, Milwaukee, Rochester, and Philadelphia, StepByStep and Pediatric Emergency Care Applied Research Network (PECARN) CDAs (13–16). These CDAs, unlike NICE, aim to identify febrile infants at low risk of SBI that can be safely managed in a community setting without parenteral antibiotics. Recent validation of the StepByStep and PECARN CDAs reported better specificity and negative predictive values (NPV) with an ability to identify over 45% of febrile infants considered to be low risk (See table1)(3,4). None of these CDAs have been validated in the UK and Ireland and they are not currently in widespread use in the UK and Ireland. More recently the American Academy of Pediatrics (AAP) released its guidance on the evaluation and management of well-appearing febrile infants 8 to 60 days old (17). As this was released in 2021, the AAP CDA has not undergone validation.

All of the CDAs make use of a range of clinical tests including urinalysis, white cell counts (WCC), absolute neutrophil counts (ANC) and C-reactive protein (CRP). None of these clinical test in isolation are diagnostic for SBI and identification of low-risk febrile infants(9). The newer CDAs (StepByStep, PECARN and AAP) include the biomarker Procalcitonin (PCT) (3,4). PCT is the precursor for calcitonin and is produced by parafollicular cells. It is a 116-amino acid protein that has roles in calcium metabolism. PCT is elevated during infection and typically rises within two hours of the onset of a bacterial infection. PCT has been shown to be highly sensitive and specific when used in the assessment of febrile infants (3,4,18–21).

Practice variation in the management of febrile infants has been documented in other jurisdictions, particularly around diagnostic evaluation in those 28 – 90 days of age(22–24). This practice variation has not been fully assessed in UK and Ireland. Also, the role of PCT and other novel biomarkers has not been, evaluated nor has there been validation studies to test the applicability of international CDAs. Understanding the practice variation and diagnostic aids in the management of febrile infants under 90 days would have the potential to improve antimicrobial stewardship, reduce costs, reduce length of stay and minimise the need for invasive procedures such as lumbar punctures.

Table 1: Validated Clinical Decision Aids (CDAs).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | PECARN | Step-by-Step | NICE NG143 | NICE 51 | BSAC | AAP |
| Region | USA | Europe | UK & Ireland | UK & Ireland | UK & Ireland | USA |
| Age | < 60 days  | < 90 days  | < 90 days  | < 90 days | < 90 days | 8 – 60 days old |
| Validation cohort | 913 | 2185 | 555 | 555 | 555 | NV |
| Study population | All febrile infants (not critically ill, premature, received antibiotics in 24hrs or with indwelling devices) | -Well appearing febrile infants-Fever without source | All febrile infants | All febrile infants | All febrile infants | Well-appearing febrile infants (not critically ill, premature, received antibiotics in 24hrs or with indwelling devices) |
| Biomakers | ANC, PCT | ANC, CRP, PCT | CRP | CRP | CRP | ANC, PCT |
| Sensitivity % (95% CI) | 97.7 (91.3-99.6) | 92.0 (84.3–96.0) | 91 (82 – 96) | 100 (95 – 100) | 82 (72 – 90) | NV |
| Specificity % (95% CI) | 60.0 (56.6-63.3) | 46.9 (44.8–49.0) | 9 (7 – 12) | 0 (0 – 1) | 14 (11 – 17) | NV |
| PPV % (95% CI) | 20.7 (16.9-25.0 | 6.7 (5.4–8.3) | 14 (11 – 17) | 14 (11 – 17) | 13 (11 – 17) | NV |
| NPV % (95% CI) | 99.6 (98.4-99.9) | 99.3 (98.5–99.7) | 86 (74 – 94) | N/A | 82 (72 – 90) | NV |
| Low cohort risk identified (%) | 497 (54) | 991 (45.3) | 51 (9) | None | 80 (14) | NV |
| *National Institute for Health and Care Excellence (NICE), Pediatric Emergency Care Applied Research Network (PECARN), British Society for Antimicrobial Chemotherapy (BSAC), American Academy of Pediatrics (AAP) Absoulute Neutrophil Count (ANC), C-Reactive Protein (CRP), Procalcitonin (PCT), Postive Predictive Value (PPV), Negative Predictive Value (NPV), Not Validated (NV)* |  |

# Rationale

The aim of the FIDO study is to prospectively validate a range of CDAs in a UK and Irish population including CDAs that utilise PCT testing i.e. StepByStep, PECARN and AAP.

# Objectives

## Primary Objectives

* Report the aetiology of SBI in febrile infants under three months in UK and Ireland.
* Describe the clinical and laboratory predictors of SBI in febrile infants under three months of age.
* Report the performance accuracy of UK clinical practice guidelines for the assessment and management of febrile infants.

## Secondary Objectives

* Report the performance accuracy of international clinical practice guidelines for the assessment and management of febrile infants.
* Report a cost analysis for the different approaches.
* Report parents/guardians and clinicians’ views on how best to communicate different treatment strategies including risks and benefits of each.
* Store residual blood specimens for future biomarker discovery.

# Study Design

A multicentre observational prospective cohort study in the UK and Ireland conducted via Paediatric Emergency Research in the UK and Ireland (PERUKI). This protocol has been produced as to adhere to the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) (25).

## Study Population

All infants 90 days of age and under with a fever of ≥38oC during their time in the Emergency Department (ED) or Assessment Unit (AU) or with a history of fever of ≥38oC recorded by anyone via any thermometer type within the last 24 hours. There are no exclusion criteria, but data will be recorded regarding gestational age, antenatal complications, underlying health conditions and recent admissions to hospital.

## Setting

30 PERUKI sites across the UK and Ireland.

## Screening

The first approach will be by members of the clinical team caring for the patient. Eligible participants will be screened by appropriately trained clinical staff, using the case report form (CRF). The CRF will be used to record non-personal data such as baseline demographic data, clinical features and initial examination findings. A linkage log will be stored securely at each site; this will contain the study ID (cross referenced against patient identifiable details). The principal investigator and nominated deputies will control access to this linkage document. An example of the CRF is available as supplementary material.

## Procedures

All eligible participants will be enrolled. In all instances routine care will not be interrupted. Where possible an additional 1ml of blood will be taken and stored for biomarker discovery and validation. This blood will be collected during routine phlebotomy. There will be no additional phlebotomy events beyond those required for routine clinical care. Seven days after discharge the CRF will be completed by a trained member of the local study team. This will involve reviewing the medical records and a phone call (maximum of three attempts) to the parent/guardian to determine if there had been any subsequent unplanned re-attendances to hospital.

**Infant under 90 days of age with fever ≥38 0C in the last 24 hours**

**Time (minutes)**

0

10

**Medical assessment including routine bloods and urinalysis. Additional investigations as per attending clinician.**

**(No additional phlebotomy events beyond standard care)**

20

30

If available 1 ml of blood saved for future biomarker testing

40

50

**Treatment**

**given as per standard care without delay**

CRF started contemporaneously by clinical staff

60

 ***Patient transferred from ED when appropriate – child may be admitted or discharged as the attending clinician.***

**Admitted**

**Discharged**

Within 24 of screening

If still an inpatient, then the child

is followed up on the wards by a member of the research team to obtain deferred consent (when necessary) and complete CRF

If patient has been discharged, then

child is followed up by phone call from a member of the research team to obtain deferred consent (when necessary).

7 days after discharge

CRF completed with laboratory test results and follow up complete

***Figure 1 Flow diagram of study procedure***

## Blood Plasma Collection and Storage

During routine phlebotomy 1ml of additional blood plasma will be collected for additional biomarker discovery and validation. No additional phlebotomy events will be performed beyond those required for usual care. All patients in the study will receive clinical care without delay as per local guidance and clinician practice. The 1ml of blood plasma taken during routine phlebotomy will be collected for biomarker analysis. If insufficient blood is available, then routine testing will be prioritised. The specimens will be stored at local sites and transported to the research laboratory in Wellcome-Wolfson Institute for Experimental Medicine (WWIEM), Queen's University Belfast. Transport of samples to WWIEM will only occur once written consent has been provided. If no consent is gained samples will not be transported and destroyed at site level. A full list of procedures can be seen in Table 2.

Table 2: Study Assessments

|  |  |  |
| --- | --- | --- |
|  | **At Presentation** | **Follow-up** |
| **<4 hours** | **0-24 hours**  | **7 days after discharge** |
| Screening and data entry CRF | X |  |  |  |
| 1ml of blood sent for storage |  | X | X |  |
| Consent discussion |  | X | X |  |
| Notes review and CRF checking by member of research team |  |  | X |  |
| Notes review and CRF completion by member of research team |  |  |  | X |

## Reference Standards

The reference standard is the diagnosis of a serious bacterial infection (SBI) including meningitis, bacteremia and urinary tract infection (excluding contaminants).

**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).

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

**Bacteremia** 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 suspected diagnosis.

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

## 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 GCP training. Clinical data and outcome will be recorded on the case report forms (CRF) or directly onto an electronic database. The CRF and linkage logs will be kept in a pre-designated 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 and use of the data will need pre-authorization from study investigators. Pseudoanonymisation will be necessary at site level to enable data queries and audit research purposes. The CRF will be uploaded to 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 Good Clinical Practice and the European General Data Protection Regulation on data management (27,28). Paper copies of the CRF will be available as a back-up. All data uploaded to REDCap database will be anonymised, non-personal data.

## Consent

Febrile infants are at high risk of SBI and sepsis. Their initial assessment and management is a medical emergency. It is therefore not possible, or appropriate, to discuss research during the initial assessment and resuscitation phase. For this study we will utilise the Research Without Prior Consent (RWPC) methodology. 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 (PiC) study (29,30). RWPC has also been used in the EcLiPSE trial undertaken by PERUKI (31). In all instances consent to include data and blood plasma in the study will be sought at the earliest appropriate opportunity. No blood testing will be performed on the blood plasma sample for research without prior consent. If consent is declined, then the blood plasma sample and clinical data will be excluded from the study.

### Face to Face Consent Discussions

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 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. In situations where the researcher is not part of the clinical team, a member of the clinical team will first check with the parents that it is ok for the researcher to discuss consent. Once approval is gained the member of the clinical team will introduce the researcher to the parents.

### Virtual Consent Discussion

Some participants will be discharged before face to face consent discussions can take place. 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 participant information and consent forms by post/email. Verbal consent will be documented and if any parent declines consent verbally their details will not be included in the study. Electronic signatures will also be accommodated if the parent prefers to use that option. If after four weeks there is no response another pack participant information sheet and consent form will be sent in the post/email. If no reply is received after four weeks participant routinely collected data will be included in the study. However, written informed consent will be needed for the use of blood samples. Only 2 packs in total will be sent out to parents of participants, a third letter will not be sent out.

### Providing Study Information

A member of the research team will explain to parents the reasons why informed consent cannot be sought in emergency care research.

A member of the research team will also discuss with the parent the:

* Objectives
* Risks and inconveniences of the study
* Conditions under which it is to be conducted
* Emphasise that participation in the study is voluntary and that the participant may withdraw from the study at any time and for any reason.

The parent/guardian will be provided with the appropriate participant information and consent forms (see appendices) and will be asked to read and review the document. Upon reviewing the document, all participants will be given the opportunity to ask any questions that may arise, have the opportunity to discuss the study with their surrogates and have time to consider the information prior to agreeing to participate. A contact point where further information may be obtained will be provided. Parents/guardians should decide whether or not to join the study ideally within 24 hours of attending the ED.

### Consent/Assent Form Completion

The parent/guardian will sign and date the electronic/written consent form. Once the parent/guardian has signed the consent form, the person obtaining consent will countersign the form. Copies of the fully completed consent forms will be given to the parent/guardian for their records. A copy will be filed in the participant’s medical notes. Copies of the consent/assent form will also be kept with the PI at each site in a locked filing cabinet.

### Death Prior to Consent

This is likely to be a rare occurrence but almost certainly will occur. When a participant dies before consent has been sought, the site PI or nominated deputy will obtain information from clinical colleagues and establish the most appropriate practitioner to notify parents of the research involvement. Consent can be sought from parents 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 if this 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 the parents to a meeting with the consultant in charge of their child’s care after a death. This usually takes place some days/weeks after death. At this meeting the consultant will be asked to explain the study, reasons for research without prior consent (deferred consent), how to opt in or out of the study and provide contact details if parents/guardian wish to discuss the study with a member of the research team (either in person or by telephone). Following the meeting a period of four weeks will be allowed for the family to contact the research team. No communication in the form of an email/letter will be sent to the bereaved parents without prior introduction or explanation by clinical team of the research being undertaken and reason for deferred consent. If no contact is made, then a personalised letter/email including the participant information sheet and consent form will be sent to the bereaved family (Bereaved Letter 1). This letter will explain the study, reasons for research without prior consent (deferred consent), 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 by telephone). If after another four weeks after sending the initial letter/email to the bereaved family, there is no response, a follow up letter/email along with the participant information sheet and consent form will be sent to the bereaved family (Bereaved Letter 2). This second letter will explain the study, reasons for research without prior consent (deferred consent), 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 by telephone). In addition, this letter/email will also confirm that if no consent form is received within four weeks of the letter being sent then only the participant’s anonymised data will be included in the study. Blood samples collected for the purpose of the study will not be included in the study, unless the family notify the site team otherwise. This approach is based on CONNECT guidance for conducting research without prior consent in children (32). CONNECT guidance is an evidence-based guideline for the use of research without prior consent in children. Section 5 of this guidance specifically describes how best to approach the issue of research without prior consent following the death of a child (32).

### Discharge/Transfer Prior to Consent being sought

Wherever possible consent will be obtained prior to discharge. In some instances, the child may be discharged from ED or the ward prior to consent being obtained. In these instances, a member of the research team will call the parent/guardian and explain the study, reasons for research without prior consent (deferred consent) and how to opt in or out of the study. Following this conversation, a letter/email will be sent to explain the study, reasons for research without prior consent (deferred consent), 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 by telephone). In addition, this letter/email will also confirm that if no consent form is received within four weeks of the letter being sent then only the participant’s anonymised data will be included in the study. Blood samples collected for the purpose of the study will not be included in the study, unless the family notify the site team otherwise. If a member of the research team cannot reach the parents by phone following three attempts a letter/email will be sent to explain the study, reasons for research without prior consent (deferred consent), 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 by telephone In addition, this letter/email will also confirm that if no consent form is received within four weeks of the letter being sent then only the participant’s anonymised data will be included in the study. Blood sample collected for the purpose of the study will not be included in the study, unless the family notify the site team otherwise.

### 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 that withdraw consent to participate in the study.

## Risks and Benefits

There are no benefits from taking part in this study. There is very little risk involved in this study. All participants receive usual care without delay and there are no additional procedures. All personal data is stored onsite by the principle investigator and only routinely collected, non-personal anonymised clinical data is shared with the study team.

# Statistical Analysis

This will be a convenience sample cohort study. From pilot retrospective work in 6 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 work was conducted over a 12 month period and site recruitment ranged from 45 to 151 participants per site(5). We aim to recruit from 30 PERUKI sites. It is anticipated that in 12 months it will be possible to screen 2000 febrile infants with 200-300 with stored blood for biomarker analysis. Based prior data we assume sensitivity of 95% and SBI rate of 15%, to detect 10% difference between 2 CDAs with an alpha of 0.05 with beta of 80%. Therefore, we will need approximately 1000 participants recruited. As stipulated above we hope to recruit above this number if resources enable us to do so. This will increase the statistical power and precision of our findings.

The demographic characteristics, vaccination status, risk factors, parenteral antibiotic use, admission to hospital, admission to intensive care units, and survival of the FIDO study population will be presented as descriptive statistics. 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 χ² 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 converted to categorical data and classified as within or outside published normal ranges. All predictors showing a significant association with SBI (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.

## Health Economic Evaluation

A decision analytic model will be constructed to compare the costs of the different approaches. The cost comparison analysis will be conducted from the perspective of the NHS and include costs associated with hospital resource use for the diagnosis and inpatient care of study participants using a case-mix group approach. Resource use for different groups will be assessed and costed in UK Sterling (£) using unit costs from the National Schedule of Reference Costs 2017–2018 of NHS Trusts and Primary Care Trusts combined (33). Average costs per patient to the NHS will be estimated.

## Embedded Qualitative Study

The 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 be used to explore parents’ experience of emergency care and to understand how clinicians should structure their conversations around the risk and benefits of different treatment strategies. Interviews with clinicians will explore how information about the care provided was communicated including communicating the potential risk and harms of different treatment strategies, as well as how is risk communicated to parents and families of febrile children. Supervised by Dr Kerry Woolfall, we will use findings to understand which of the different treatment strategies is most acceptable to parents and guardians and develop a framework for structuring clinical conversations, including how to communicate the risks and benefits of different treatment strategies.

Parents and guardians who decline consent for other aspects of the FIDO study, can still consent for the interviews. Those who consent for the interview and are selected will be invited to participate in a qualitative interview at a later date (within one month).

### 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 take part in an interview via face-to-face, telephone or online platform (e.g., Zoom). The parents will also be asked to sign the consent form if they wish to partake in the qualitative interviews. A trained member of the research team will make contact with families to arrange interviews within one month of providing consent. The research team member will begin the telephone interview by confirming with the person they are interviewing is the intended participant, before explaining the aims of the study and providing an opportunity for questions. Prior to initiating the interview consent will be reconfirmed both verbally and cross checked against signed consent from initial consultation.

Clinicians who register 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 interview. Interviews will take place face-to-face, online (via zoom) or via telephone.

### Sampling

Based on previous research in this area we anticipate interviewing approximately 20 parents/guardian. A further 5 to 10 clinicians will be invited for 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 and fathers and clinicans from a range of sites) and quality of dialogue to guide how many interviews to conduct. 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 just the participants name and contact details. No clinical data for the will be accessible or transferred to the interviewer beyond previously stated details for the interviews.

### Interview conduct

All interviews will be conducted by trained members of the research team supervised by Dr Woolfall. 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 (appendix) 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 individuals 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, whilst analysis will be informed by the constant comparison approach of grounded theory, the focus will be modified to fit with the criterion of catalytic validity, whereby findings should be relevant to future research and practice.

# Patient and Public Involvement (PPI)

A PPI advisory group has been formed. The advisory group supports the objectives and process of the study protocol and agree with the RWPC approach suggested. The PPI group will be involved in all aspects of the study, particularly in the development of patient resources which include the information sheets, posters and consent forms.

# Adverse Events

There are no additional interventions in this study and as such any adverse events would occur as part of standard care and should be reported as per local incident reporting policy.

# Ethical Considerations

We are planning to recruit children whom the attending doctor has identified as at high risk for sepsis. These children undergo a standard set of investigations. This includes taking samples of blood (approximately 3-5ml).

All of the children in this study will be under three months of age and will not be able to give assent and we will rely entirely parental/guardian consent. Because the assessment and initial management of suspected sepsis requires a certain degree of urgency, we will be obtaining consent after samples have been taken (research without prior consent (deferred consent).

## Sampling Issues

During phlebotomy we will store 1ml of blood. No child will undergo additional phlebotomy just to collect study specimens. If, as occasionally happens, only a very small sample of blood can be obtained, priority will be given to ensuring routine samples reach the laboratory.

## Consenting Issues

Prospective informed consent cannot be sought for FIDO as potential sepsis is a medical emergency and there is insufficient time to obtained informed consent within the therapeutic window (complete all investigations and initiate life-saving treatment within sixty minutes of attending hospital). The staff priorities are the assessment of the airway, breathing circulation with the establishment of intravenous access and a brief clinical history followed by administering treatments such intravenous antibiotics and fluids (11). Prior research conducted by the study team have demonstrated that parents do not want to discuss consent during the acute emergency nor do they have the capacity to discuss consent at this time (30,34–36). For these reasons the consent discussions will take place at the earliest appropriate opportunity (typically within 24 hours). A previous, similarly designed study known as the Petechiae in Children (PiC) [Reference 17/NI/0169] study was performed by the Chief Investigator (Dr Thomas Waterfield)(29,37). This study assessed rapid diagnostic tests for the assessment of meningococcal sepsis in children. In the PiC study the approach to deferred consent proposed here was utilised as it has been in other Paediatric Emergency Medicine (PEM) trials (31,38). This included the inclusion of data and residual blood samples from individuals who do not return written consent forms (29,31,38) as long as three attempts had been made to contact the parent/guardian by phone and that two letters had been sent to the listed address at least one month part. Embedded qualitative research conducted during the PiC study demonstrated this was acceptable on the condition that the child did not undergo any additional procedures i.e. phlebotomy (30). In the FIDO study no child will undergo any additional procedures beyond those required for their clinical care and samples will not be stored for future use beyond the study unless explicitly consented for in writing.

## Ethical Approval

This study will be submitted for ethical approval to the NHS/HSC Research Ethics Committee (REC).

# Registration

The FIDO study will be registered at the <https://www.clinicaltrials.gov> once approval for PERUKI attained.

# Dissemination

It is our intention that this data will be presented at internal and external educational/ academic meetings and in a publication in high impact medical journals. In all presentations and publications only non-identifiable, pooled results will be presented. We hope the information will inform practice in and guideline development.

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# References

1. Woll C, Neuman MI, Aronson PL. Management of the Febrile Young Infant. Pediatr Emerg Care. 2017;33(11):748–53.

2. Watt K, Waddle E, Jhaveri R. Changing epidemiology of serious bacterial infections in febrile infants without localizing signs. PLoS One. 2010;5(8):1–7.

3. Kuppermann N, Dayan PS, Levine DA, Vitale M, Tzimenatos L, Tunik MG, et al. A Clinical Prediction Rule to Identify Febrile Infants 60 Days and Younger at Low Risk for Serious Bacterial Infections. JAMA Pediatr. 2019;173(4):342–51.

4. Gomez B, Mintegi S, Bressan S, Da Dalt L, Gervaix A, Lacroix L. Validation of the “step-by-step” approach in the management of young febrile infants. Pediatrics. 2016;138(2).

5. Waterfield T, Lyttle MD, Munday C, Foster S, McNulty M, Plat R, et al. Validating clinical practice guidelines for the management of febrile infants in the United Kingdom and Ireland. Arch Dis Child. 2021;1–20.

6. Baker MD, Avner JR, Bell LM. Failure of infant observation scales in detecting serious illness in febrile, 4- to 8-week-old infants. Pediatrics. 1990;85(6):1040–3.

7. McCarthy PL, Lembo RM, Fink HD, Baron MA, Cicchetti D V. Observation, history, and physical examination in diagnosis of serious illnesses in febrile children ≤24 months. J Pediatr. 1987;110(1):26–30.

8. Nigrovic LE, Mahajan P V., Blumberg SM, Browne LR, Linakis JG, Ruddy RM, et al. The yale observation scale score and the risk of serious bacterial infections in febrile infants. Pediatrics. 2017;140(1):1–8.

9. Díaz MG, García RP, Gamero DB, González-Tomé MI, Romero PC, Ferrer MM, et al. Lack of Accuracy of Biomarkers and Physical Examination to Detect Bacterial Infection in Febrile Infants. Pediatr Emerg Care. 2016;32(10):664–8.

10. National Institute for Health and Care Excellence. Fever in under 5s: assessment and initial management NICE guideline [NG143]. NICE Guidel Online [Internet]. 2019;(November 2019):1.1.6. Available from: https://www.nice.org.uk/guidance/ng143/chapter/Recommendations

11. National Institute for Health and Care Excellence. Sepsis: recognition, diagnosis and early management. NICE guideline [NG51]. NICE Guid Online [Internet] [Internet]. 2020;(July 2016). Available from: https://www.nice.org.uk/guidance/ng51/resources/sepsis-recognition-diagnosis-and-early-management-pdf-1837508256709

12. Sanjay Patel, Robert Cunney A, Demirjian, Conor Doherty, Helen Green, Mathew Mathai, Paddy McMaster A, Munro, Stéphane Paulus, Andrew Taylor DR. Paediatric Common Infections Pathways: Improving antimicrobial stewardship and promoting ambulation for children presenting with common infections to hospitals in the UK and Ireland. https://bsac.org.uk/ [Internet]. 2020;(October). Available from: https://www.bsac.org.uk/wp-content/uploads/2020/10/PaediatricPathways\_ConsultationCopy.pdf

13. Baker M.D, Bell L.M AJ. Outpatient Managment Without Antibiotics Of Fever in Selected Infants. N Engl J Med. 1993;329(20):1442–8.

14. Jaskiewicz JA, McCarthy CA, Richardson AC, White KC, Fisher DJ, Dagan R, et al. Febrile infants at low risk for serious bacterial infection - An appraisal of the Rochester criteria and implications for management. Pediatrics. 1994;94(3):390–9.

15. Dagan R, Sofer S, Phillip M, Shachak E. Ambulatory care of febrile infants younger than 2 months of age classified as being at low risk for having serious bacterial infections. J Pediatr. 1988;112(3):355–60.

16. Baskin MN, O’Rourke EJ, Fleisher GR. Outpatient treatment of febrile infants 28 to 89 days of age with intramuscular administration of ceftriaxone. J Pediatr. 1992;120(1):22–7.

17. Pantell RH, Roberts KB, Adams WG, Dreyer BP, Kuppermann N, O’Leary ST, et al. Evaluation and Management of Well-Appearing Febrile Infants 8 to 60 Days Old. Pediatrics. 2021;148(2):e2021052228.

18. Gangoiti I, Fernandez CL, Gallego M, Gomez B, Benito J, Mintegi S. Markers for invasive bacterial infections in previously healthy children. Am J Emerg Med [Internet]. 2021;48:83–6. Available from: https://doi.org/10.1016/j.ajem.2021.04.018

19. Gomez B, Diaz H, Carro A, Benito J, Mintegi S. Performance of blood biomarkers to rule out invasive bacterial infection in febrile infants under 21 days old. Arch Dis Child. 2019;104(6):547–51.

20. Waterfield T, Maney JA, Hanna M, Fairley D, Shields MD. Point-of-care testing for procalcitonin in identifying bacterial infections in young infants: A diagnostic accuracy study. BMC Pediatr. 2018;18(1):1–6.

21. Gomez B, Bressan S, Mintegi S, Da Dalt L, Blazquez D, Olaciregui I, et al. Diagnostic value of procalcitonin in well-appearing young febrile infants. Pediatrics. 2012;130(5):815–22.

22. Rogers AJ, Kuppermann N, Anders J, Roosevelt G, Hoyle JD, Ruddy RM, et al. Practice Variation in the Evaluation and Disposition of Febrile Infants ≤60 Days of Age. J Emerg Med [Internet]. 2019;56(6):583–91. Available from: https://doi.org/10.1016/j.jemermed.2019.03.003

23. Jain S, Cheng J, Alpern ER, Thurm C, Schroeder L, Black K, et al. Management of febrile neonates in US pediatric emergency departments. Pediatrics. 2014;133(2):187–95.

24. Aronson PL, Thurm C, Alpern ER, Alessandrini EA, Williams DJ, Shah SS, et al. Variation in care of the febrile young infant,90 days in us pediatric emergency departments. Pediatrics. 2014;134(4):667–77.

25. Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD Statement. BMC Med. 2015;13(1):1–10.

26. Andreazza AC, Laksono I, Fernandes BS, Toben C, Riederer P, Kennedy SH, et al. HHS Public Access. 2020;20(5):340–51.

27. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–81.

28. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O’Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95(April).

29. Waterfield T, Maney JA, Fairley D, Lyttle MD, McKenna JP, Roland D, et al. Validating clinical practice guidelines for the management of children with non-blanching rashes in the UK (PiC): a prospective, multicentre cohort study. Lancet Infect Dis. 2020;3099(20):1–9.

30. Waterfield T, Lyttle MD, Shields M, Fairley D, Roland D, McKenna J, et al. Parents’ and clinicians’ views on conducting paediatric diagnostic test accuracy studies without prior informed consent: Qualitative insight from the Petechiae in Children study (PiC). Arch Dis Child. 2019;104(10):979–83.

31. Lyttle MD, Rainford NEA, Gamble C, Messahel S, Humphreys A, Hickey H, et al. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. Lancet. 2019;393(10186):2125–34.

32. CONNECT advisory group. Research without prior consent (deferred consent) in trials investigating the emergency treatment of critically ill children: CONNECT study guidance Version 2 updated July 2015 http://www.liv.ac.uk/psychology-health-and-society/research/connect/. 2015;(July).

33. NHS Reference Costs 2017–18. Approved Costing Guidance Department of Health. Dep Heal London, UK. 2018;

34. Woolfall K, Shilling V, Hickey H, Smyth RL, Sowden E, Williamson PR, et al. Parents’ Agendas in Paediatric Clinical Trial Recruitment Are Different from Researchers’ and Often Remain Unvoiced: A Qualitative Study. PLoS One. 2013;8(7).

35. Woolfall K, Young B, Frith L, Appleton R, Iyer A, Messahel S, et al. Doing challenging research studies in a patient-centred way: A qualitative study to inform a randomised controlled trial in the paediatric emergency care setting. BMJ Open. 2014;4(5):1–11.

36. Woolfall K, Frith L, Gamble C, Gilbert R, Mok Q, Young B. How parents and practitioners experience research without prior consent (deferred consent) for emergency research involving children with life threatening conditions: A mixed method study. BMJ Open. 2015;5(9):1–14.

37. Waterfield T, Lyttle MD, Fairley D, Mckenna J, Woolfall K, Lynn F, et al. The “Petechiae in children” (PiC) study: Evaluating potential clinical decision rules for the management of feverish children with non-blanching rashes, including the role of point of care testing for Procalcitonin & Neisseria meningitidis DNA - a study p. BMC Pediatr. 2018;18(1):1–9.

38. Rochwerg B, Millen T, Austin P, Zeller M, D’Aragon F, Jaeschke R, et al. Fluids in Sepsis and Septic Shock (FISSH): Protocol for a pilot randomised controlled trial. BMJ Open. 2017;7(7):1–5.