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TITLE

Parental and Healthcare Professional Concern in the Diagnosis of Paediatric Sepsis: A Protocol for a Prospective Multicentre Observational Study

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KEYWORDS: Sepsis; Paediatrics; Intuition; Emergency Service, Hospital; Infection

WORD COUNT: 2779

ABSTRACT

Introduction Paediatric sepsis is a major contributor to morbidity and mortality worldwide. Assessing concern from parents and healthcare professionals to determine disease severity in a child being evaluated for sepsis represents an under-established field. This study aims to determine the diagnostic accuracy of parental and healthcare professional concern in the diagnosis of children evaluated for sepsis.

Methods and analysis This prospective multicentre observational study will be conducted over a 12-month period in paediatric Emergency Department (ED)s at two tertiary Australian hospitals. A cross-sectional survey design will be utilised to assess the level of concern of parents, nurses and doctors for children presenting to ED and assessed for sepsis. The primary outcome is diagnosis of sepsis defined as suspected infection plus organ dysfunction at time of survey completion. Secondary outcomes include suspected or proven infection and development of organ dysfunction, defined as a pSOFA score >0, within 48hours of presentation, and confirmed or probable bacterial infection independent of organ dysfunction. New knowledge generated from the study may contribute to the earlier recognition and treatment of paediatric sepsis.

Ethics and dissemination Ethics approval was obtained from the institutional ethics Committee (HREC/17/QRCH/85). Findings will be shared with relevant stakeholders and disseminated via conferences and peer-reviewed journals.

Universal trial number: U1111-1256-4537 pre-results

Keywords: Sepsis; Paediatrics; Children; Intuition; Emergency Service, Hospital; Infection

Strengths and limitations of this study:

- Prospective assessment of parental, nursing, and medical concern will be undertaken both quantitatively and qualitatively.
- Embedding the study in an established institutional paediatric sepsis pathway reduces barriers for staff engagement.
- Although this is the largest study on parental and healthcare professional concern in recognising paediatric sepsis, consideration for other sources of diagnostic bias as a result of referral, previous history, and concomitant interventions is required.

INTRODUCTION

Sepsis is a major contributor to morbidity and mortality in children worldwide. (1) The World Health Organisation recently identified sepsis as a key health priority, outlining the high global burden of this time critical and often preventable disease. (2) While the latest definition of paediatric sepsis dates back to 2005, (3) the definition of sepsis in adults was re-defined in 2016 as 'life threatening organ dysfunction caused by a dysregulated host response to infection'. (4) Globally, close to 50 million patients suffer from sepsis each year, with over 10 million sepsis-related deaths, (5) the highest incidence affecting infants and children. The average cost of a severe sepsis hospitalisation in the United States averages approximately $26,592 USD, accounting for a total cost of $7.31 billion dollars nationwide. (6) These high economic costs, along with the increasing prevalence and morbidity of paediatric sepsis, highlight the urgent need for further research into earlier sepsis recognition.

Prompt identification is well recognised as fundamental for the early intervention and treatment of sepsis. In a large retrospective study of children with sepsis, the delay in the administration of a sepsis treatment bundle consisting of intravenous antibiotics, fluids and blood cultures was associated with a significant increase in mortality. (7) The majority of paediatric sepsis deaths occur within the first 48 hours of initial admission to the Intensive Care Unit, (8) emphasising the need for prompt recognition and resuscitation. The new Surviving Sepsis Guidelines (9) further iterate the need for early detection as it is a critical survival factor for paediatric sepsis, with timely and appropriate initiation of interventions being linked to improved patient outcomes.

Paediatric sepsis is an insidious condition which poses many challenges for healthcare professionals to accurately and timely diagnose. This is due to the vague and non-specific nature of the disease coupled with a relatively low incidence rate compared to the number of children presenting to the Emergency Department (ED) with febrile illness. (10) This low incidence of sepsis presents a challenge akin to finding a 'needle in a haystack' for clinicians. Consequently, the risk for a missed or misdiagnosis is high and subsequent repercussions are potentially lifelong and fatal. (11) In its early stages, sepsis often resembles many other common febrile illnesses with the clinical signs of fever, tachycardia and tachypnoea. (12)

Parents, as experts of their child, may be valuable in the identification of sepsis and discrimination of the condition as opposed to other milder illnesses.

Observational studies suggest that parents may recognise illness severity before nurses and doctors, independent of key clinical signs. (13) Root-cause-analyses and anecdotal data after fatal paediatric sepsis outcomes established that children often re-presented several times and parents commonly indicated concerns that the "illness was different". (13) A more holistic and family-centred-care approach incorporating collaboration between the child's family and treating team has the potential to enhance the timely recognition of sepsis. (14)

The current diagnostic model for sepsis relies predominately on objective tools, which pose numerous challenges due to the complex nature of paediatric physiology. (15) While the search for more precise biomarkers for sepsis continues, little is known in relation to utilising concern as a diagnostic tool to aid in earlier recognition. (16) In addition to parental concern, the gut feeling or intuition of healthcare professionals may contribute to the recognition of sepsis. (17) In the primary care setting, a gut feeling that "something was wrong" reported by clinicians was linked with a high specificity and positive likelihood ratio for serious bacterial infections. (18) The inclusion of parental and healthcare worker concern in the diagnostic model has the potential ability to improve specificity, thereby increasing sepsis recognition and earlier treatment.

It is hypothesised that the inclusion of parental and healthcare professional concern in the ED will improve diagnostic accuracy and early recognition of paediatric sepsis. The main objective of this study is to determine the diagnostic accuracy of concern levels in parents, doctors and nurses to recognise paediatric sepsis in a prospective multicentre observational study.

METHODS AND ANALYSIS

Study Design

This prospective multi-centre observational cohort study will use a cross-sectional survey tool designed to independently assess the level of concern of parents, nurses and doctors for children who present to the ED and are evaluated for sepsis. The study will run for 12 months and will attempt to meet the criteria for diagnostic accuracy studies (STARD). (19)

Study setting

This study will be conducted across the dedicated paediatric EDs at two tertiary Australian hospitals: Queensland Children's Hospital (QCH), which receives approximately 6600 presentations each month, and Gold Coast University Hospital (GCUH), which receives approximately 2300 paediatric presentations each month.

Participants

Eligible participants will be children aged between 30 days to 18 years presenting to the ED and evaluated for sepsis via the institutional sepsis pathway and/or undergo blood culture sampling for suspected infection.

Study Criteria

Participants will be selected using the eligibility criteria outlined in table 1.

Inclusion criteria	Exclusion criteria
• Child aged 30 days to 18 years old • Presented to ED • Evaluated for sepsis on the sepsis pathway and/or having blood culture sampling • Survey completed during ED stay, aiming to be completed at time closest to triage presentation. • Parent/Care-giver attending with child, treating doctor and/or nurse available for survey	• Parents who speak languages other than English • Children with high suspicion of SARS-CoV-2 infection • Patients in clinical areas outside the ED such as Paediatric Intensive Care Unit

Table 1: Study inclusion and exclusion criteria

Test Methods:

The study surveys have been individually designed for parents, nurses and doctors, incorporating both quantitative and qualitative measures (Figures 1a, 1b and 1c). To ensure consistent comparison, all surveys have the same basic design and content, with minor adaptions to reflect the participant role (parent vs nurse vs doctor). Participants are asked to rate the degree to which they agree or disagree with a statement or question using a 5-point Likert scale, (20) followed by two free text questions. This method of testing was chosen due

to the advantage of the survey facilitating questions in a straightforward and simple manner, which will be pragmatic for respondents to use, a critical requirement for recruitment in an ED setting. The surveys were piloted 20 times to ensure questionnaire feasibility. Job title and years of experience for participating doctors and nurses will be collected. (17)

The surveys will be distributed to one of the child's parents/caregiver's, nurse and doctor on presentation and will be completed during ED stay. Surveys will aim to be completed at time closest to triage and within 4-hrs from initial presentation. This window for survey administration was determined based on the current Australian National Emergency Assess Target guidelines which stipulate that patients must be admitted, discharged or transferred from ED within 4 hours of initial presentation. (21) These surveys are embedded within the *Queensland Sepsis Pathway* which was developed and implemented across Queensland paediatric EDs.

Sample Size

A minimum of 400 patients will be recruited over the two sites. This minimum sample size was selected based on a sample size calculation which revealed that with an expected prevalence of 10% and an expected improvement in sensitivity from 0.6 to 0.8, a sample size of 450 is needed. (22)

Data Collection

The patient demographics, information regarding the presentation and illness severity at baseline will be collected from the medical record. In addition, the worst measure of physiological parameters and maximum level of support during the first 48 hours will be captured. Illness severity will be determined using the Paediatric Sequential Organ Failure Assessment (pSOFA) score. (23) Data will be recorded into a RedCap case report form.

Analysis Plan

Suspected or proven infection in presence of organ dysfunction, defined as a pSOFA score >0 at time of assessment, is defined as the primary outcome. Secondary outcomes include a) suspected or proven infection and development of organ dysfunction, defined as a pSOFA score >0, within 48hours of presentation; and b) confirmed or probable bacterial infection independent of organ dysfunction. The likelihood of bacterial versus viral infection will be

assessed using all available laboratory, microbiological, and clinical information with adjudication of patients (24) into *confirmed bacterial infection* (positive microbiological cultures compatible with the clinical syndrome, and decision by the treating physician to treat for at least 5 days or until death with antibiotics), *probable bacterial infection* (negative microbiological cultures in presence of a clinical syndrome of bacterial infection and increased C-reactive protein, and decision by the treating physician to treat for at least 5 days or until death with antibiotics), *probable viral infection* (negative microbiological tests in presence of a clinical syndrome of viral infection such as bronchiolitis), *proven viral infection* (positive microbiological testing in presence of a clinical syndrome of viral infection), *infection of uncertain origin*, and *non-infectious conditions*.

Descriptive analyses will report on the demographics and baseline patient features. Illness severity will be measured through the pSOFA score. Description on the level of completeness of the surveys (parental, nursing, medical) and patient characteristics will be provided and the differences in demographics will be investigated between children who have completed surveys from all three participant groups and those who have missing surveys.

First, an exploratory factor analysis will be performed on the questions used in the surveys to determine whether the questions are measuring the same latent construct, concern, or if more than one construct is present. In addition, the internal consistency and inter-rater reliability of the items will be assessed. Based on the results of the factor analysis, the questions which have the strongest factor loadings will be identified and included in the mixed effects model.

Next, a linear mixed effects model will be performed for the primary and secondary outcomes to assess the associations between the selected concern items and the outcome. A random intercept will be estimated for each child, to assess the variation in illness severity between children and a random slope for concern will also be explored for each child and each participant group, to account for the different responders per child. Other demographic and comorbidities, which are predictors of sepsis, will be included in the model as control variables. The AUROC, sensitivity, specificity, negative and positive predictive value and likelihood ratios will be calculated to assess model fit and predictive performance.

P-values below 0.05 will be considered as significant and 95% confidence intervals will be reported alongside all significant effects. All analyses will be performed by an expert statistician using R. (25)

A pre-planned secondary analysis will assess qualitative data from the survey free text questions utilising the Framework Method (Gale et al., 2013). These free texts will then be examined and sorted into multiple categories to determine commonalities and differences. These categories will then be sorted into themes for the three groups: parents, doctors and nurses. Confirmation of these themes will be in collaboration with the research team to maintain rigor, validity and transparency of analysis. (26)

Strengths

A strength of this study is its prospective observational study design with a large multicentre cohort of children evaluated for sepsis. In contrast to previous studies which more broadly captured serious bacterial infections (18) or pyrexia, (27) the present study captures sepsis defined as suspected/proven infection with organ dysfunction as the main outcome. The study design enables assessment of the role of parental and healthcare professional concern in diagnosing paediatric sepsis and compares the respective diagnostic accuracies with the diagnostic performance of the routine diagnostic process.

This study aims to address an established gap regarding the significance of parental and healthcare professional concern in predicting disease severity in children with infection. Outcomes can inform the design of improved sepsis recognition tools. While the study will be conducted within the ED, findings relating to the use of concern as a red flag and a prompt for further investigation and assessment could be translated into other clinical settings.

Limitations

This study presents several limitations. It is expected that some patients will only have partial sets of surveys completed due to circumstances such as a parent being deemed unfit to complete a research survey for various reasons, or the attending nurse or doctor not completing a survey. The incomplete sets of surveys for patients is anticipated given the pragmatic nature of the study and will be a consideration when conducting analysis and reporting. Bias could occur through children who are more clinically well having a greater number of concern surveys completed, as opposed to more clinically unwell children, whereby parents may be too

distressed and healthcare professionals otherwise occupied treating the child. (28) Standardised dissemination of study education will aim to reduce potential bias related to variances on how the surveys are administered to parents, doctors and nurses. Implementation of an educational script will eliminate the use of words such as sepsis, organ dysfunction or death which may potentially heighten concern levels or result in changes to concern.

Ethics and dissemination

Informed verbal consent will be gained from the parent/care-giver, nurse and doctor at the time of survey administration. It will be reiterated to all parties that they have the right to refuse participation at initial time of consent or withdraw at any stage without affecting patient care or their employment, as applicable. The survey and study design have been approved by the Children's Health Queensland Human Research Ethics Committee (HREC/17/QRCH/85). Findings will be shared with relevant stakeholders and disseminated via conferences and peer-reviewed journals.

Patient and public involvement

Parents have not been involved in the design of the survey tool. However, key findings will be shared via the parent-consumer representatives during dissemination at a local and national level.

Contributors: LJS conceived the project and provided the technical and intellectual inputs supporting ZS and AH in writing this manuscript and approved it for submission. ZS produced the first draft and subsequent drafts of the paper. AH and ZS lead central coordination and contributed to the design of the analysis plan. ZS, LJS, MJ, SG, TG and AH were involved in review and provided inputs on the manuscript. All authors reviewed and approved various drafts and the final paper.

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Competing interests None declared.

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Study ID: .....

Date &Time: .....

(Affix patient identification label here)

URN:

Family Name:

Given Names:

Address:

Date of Birth: Sex: ☐ M ☐ F ☐ I

Parent/Care-Giver

RAPIDS Study

We would like to ask you to participate in this study. We are interested in measuring the parental concern as a tool to predict how severe a child's illness may be. No one knows your child better than you so we ask that you please complete this short survey to indicate if/what concerns you most about your child's illness. ***By completing this survey you are consenting to us analysing this data together with information from the medical health record for research purposes.***

1. Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your child's illness:

Not Concerned	1	2	3	4	5	Extremely Concerned

2. Do you have a gut feeling that something is wrong with your child? Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your child's illness:

I feel things are ok	1	2	3	4	5	I feel something is Extremely Wrong

3. Please place an 'X' in the below fields to indicate how different is your child's behaviour right now compared to normal?

Normal Behaviour for Child	1	2	3	4	5	Extremely Abnormal Behaviour for Child

4. What are the symptoms/behaviours that your child displayed, which prompted you to bring your child to hospital? *Please list as many as possible:*

1. ..... 3. .....

2. ..... 4. .....

5. What was the symptom that concerned you the most?

.....

6. Please place an 'X' in the below fields to indicate how severe you feel your child's illness is *today?*

Mildly Unwell	1	2	3	4	5	Severely Unwell

7. Please place an 'X' in the below fields to indicate how unwell you feel your child is today compared to *how unwell they have been in the past*:

Mild Illness for Child	1	2	3	4	5	Most Severe Illness for Child

Figure 1a: Parental survey

Study ID: .....

Date &Time: .....

(Affix patient identification label here)

URN:

Family Name:

Given Names:

Address:

Date of Birth: Sex: ☐ M ☐ F ☐ I

Nursing Survey

RAPIDS Trial

We would like to ask you to participate in this study. We are interested in measuring the treating nurse's level of concern as a tool to predict how severe a child's illness may be. We ask that you please complete this short survey to indicate what concerns you most about your patient's illness. By completing this survey you are consenting to us including this data for research purposes.

Job Title (RN/CN): .....

Years of Experience: .....

1. Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your patient's illness

Not Concerned	1	2	3	4	5	Extremely Concerned

2. Do you have a gut feeling that something is wrong with your patient? Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your child's illness:

I feel things are ok	1	2	3	4	5	I feel something is Extremely Wrong

3. Please place an 'X' in the below fields to indicate how different is your patient's behaviour deviating from their norm based on your discussion with patient/parent?

Normal Behaviour for Child	1	2	3	4	5	Extremely Abnormal Behaviour for Child

4. What are the symptoms/behaviours that your patient displayed that trigger your concern?
Please list as many as possible

1. ..... 3. .....

2. ..... 4. .....

5. What was the symptom that concerned you the most?

.....

6. Please place an 'X' in the below fields to indicate how severe you feel your patient's illness is:

Mildly Unwell	1	2	3	4	5	Severely Unwell

Figure 1b: Nursing survey

Study ID: .....

Date &Time: .....

(Affix patient identification label here)

URN:

Family Name:

Given Names:

Address:

Date of Birth: Sex: ☐ M ☐ F ☐ I

Medical Survey

RAPIDS Trial

We would like to ask you to participate in this study. We are interested in measuring the treating doctor's level of concern as a tool to predict how severe a child's illness may be. We ask that you please complete this short survey to indicate what concerns you most about your patient's illness. By completing this survey you are consenting to us including this data for research purposes.

Job Title (e.g. SMO): .....

Years of Experience: .....

1. Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your patient's illness

Not Concerned	1	2	3	4	5	Extremely Concerned

2. Do you have a gut feeling that something is wrong with your patient? Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your child's illness:

I feel things are ok	1	2	3	4	5	I feel something is Extremely Wrong

3. Please place an 'X' in the below fields to indicate how different is your patient's behaviour deviating from their norm based on your discussion with patient/parent?

Normal Behaviour for Child	1	2	3	4	5	Extremely Abnormal Behaviour for Child

4. What are the symptoms/behaviours that your patient displayed that trigger your concern?
Please list as many as possible

1. ..... 3. .....

2. ..... 4. .....

5. What was the symptom that concerned you the most?

.....

6. Please place an 'X' in the below fields to indicate how severe you feel your patient's illness is:

Mildly Unwell	1	2	3	4	5	Severely Unwell

Figure 1c: Medical survey

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	#1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	#1
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	#1
	4	Study objectives and hypotheses	#2
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	#2
Participants	**6**	Eligibility criteria	#3
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	#4
	8	Where and when potentially eligible participants were identified (setting, location and dates)	#2
	9	Whether participants formed a consecutive, random or convenience series	Not specified
Test methods	**10a**	Index test, in sufficient detail to allow replication	N/A
	10b	Reference standard, in sufficient detail to allow replication	N/A
	11	Rationale for choosing the reference standard (if alternatives exist)	N/A
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	#5
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	N/A
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	N/A
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	N/A
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	#5
	15	How indeterminate index test or reference standard results were handled	N/A
	16	How missing data on the index test and reference standard were handled	N/A
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	#5
	18	Intended sample size and how it was determined	#4
RESULTS			
Participants	**19**	Flow of participants, using a diagram	#3 (no diagram)
	20	Baseline demographic and clinical characteristics of participants	N/A
	21a	Distribution of severity of disease in those with the target condition	N/A
	21b	Distribution of alternative diagnoses in those without the target condition	N/A
	22	Time interval and any clinical interventions between index test and reference standard	N/A
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	N/A
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	#5
	25	Any adverse events from performing the index test or the reference standard	N/A
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	#6
	27	Implications for practice, including the intended use and clinical role of the index test	N/A
OTHER INFORMATION			
	28	Registration number and name of registry	#1
	29	Where the full study protocol can be accessed	Only submitted, not yet accessible

	30	Sources of funding and other support; role of funders	#7

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

BMJ Open

Parental and Healthcare Professional Concern in the Diagnosis of Paediatric Sepsis: A Protocol for a Prospective Multicentre Observational Study

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TITLE

Parental and Healthcare Professional Concern in the Diagnosis of Paediatric Sepsis: A Protocol for a Prospective Multicentre Observational Study

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KEYWORDS: Sepsis; Paediatrics; Intuition; Emergency Service, Hospital; Infection

WORD COUNT: 2764

ABSTRACT

Introduction: Paediatric sepsis is a major contributor to morbidity and mortality worldwide. Assessing concern from parents and healthcare professionals to determine disease severity in a child evaluated for sepsis remains a field requiring further investigation. This study aims to determine the diagnostic accuracy of parental and healthcare professional concern in the diagnosis of children evaluated for sepsis.

Methods and analysis: This prospective multicentre observational study will be conducted over a 12-month period in paediatric Emergency Department (ED)s at two tertiary Australian hospitals. A cross-sectional survey design will be utilised to assess the level of concern of parents, nurses and doctors for children presenting to ED and assessed for sepsis. The primary outcome is diagnosis of sepsis defined as suspected infection plus organ dysfunction at time of survey completion. Secondary outcomes include suspected or proven infection and development of organ dysfunction, defined as a pSOFA score >0, within 48hours of presentation, and confirmed or probable bacterial infection independent of organ dysfunction. New knowledge generated from the study may contribute to the earlier recognition and treatment of paediatric sepsis.

Ethics and dissemination: Ethics approval was obtained from the Children's Health Queensland Human Research Ethics Committee (HREC/17/QRCH/85). Findings will be shared with relevant stakeholders and disseminated via conferences and peer-reviewed journals.

Universal trial number: U1111-1256-4537

Keywords: Sepsis; Paediatrics; Children; Intuition; Emergency Service, Hospital; Infection

Strengths and limitations of this study:

- Prospective assessment of parental, nursing, and medical concern will be undertaken both quantitatively and qualitatively.
- Embedding the study in an established institutional paediatric sepsis pathway reduces barriers for staff engagement.
- Although this is the largest study on parental and healthcare professional concern in recognising paediatric sepsis, consideration for other sources of diagnostic bias as a result of referral, previous history, and concomitant interventions is required.

INTRODUCTION

Sepsis is a major contributor to morbidity and mortality in children worldwide. (1) The World Health Organisation recently identified sepsis as a key health priority, outlining the high global burden of this time critical and often preventable disease. (2) While the latest definition of paediatric sepsis dates back to 2005, (3) the definition of sepsis in adults was re-defined in 2016 as 'life threatening organ dysfunction caused by a dysregulated host response to infection'. (4) Globally, close to 50 million patients suffer from sepsis each year, with over 10 million sepsis-related deaths, (5) the highest incidence affecting infants and children. While the highest burden related to sepsis affects low and middle income settings, sepsis remains amongst the leading causes of (potentially preventable) morbidity and mortality in high income countries too, accounting for a total cost of $7.31 billion dollars in the United States alone. (6) These high economic costs, along with the persistently high prevalence and morbidity of paediatric sepsis, highlight the urgent need for further research into earlier sepsis recognition.

Prompt identification is well recognised as fundamental for the early intervention and treatment of sepsis. In a large retrospective study of children with sepsis, the delay in the administration of a sepsis treatment bundle consisting of intravenous antibiotics, fluids and blood cultures was associated with a significant increase in mortality. (7) The majority of paediatric sepsis deaths occur within the first 48 hours of initial admission to the Intensive Care Unit, (8) emphasising the need for prompt recognition and resuscitation. The new Surviving Sepsis Guidelines (9) further emphasise the need for early detection, as it is a critical survival factor for paediatric sepsis, with timely and appropriate initiation of interventions being linked to improved patient outcomes.

Paediatric sepsis is an insidious condition which poses many challenges for healthcare professionals to accurately and timely diagnose. This is due to the vague and non-specific nature of the disease coupled with a relatively low incidence rate compared to the number of children presenting to the Emergency Department (ED) with febrile illness. (10) This low incidence of sepsis presents a challenge akin to finding a 'needle in a haystack' for clinicians. Consequently, the risk for a missed or misdiagnosis is high and subsequent repercussions are potentially lifelong and fatal. (11) In its early stages, sepsis often resembles many other

common febrile illnesses with the clinical signs of fever, tachycardia and tachypnoea. (12) Parents, as experts of their child, may be valuable in the identification of sepsis and discrimination of the condition as opposed to other milder illnesses.

Observational studies suggest that parents may recognise illness severity before nurses and doctors, independent of key clinical signs. (13) Root-cause-analyses and anecdotal data after fatal paediatric sepsis outcomes established that children often re-presented several times and parents commonly indicated concerns that the "illness was different". (13) A more holistic and family-centred-care approach incorporating collaboration between the child's family and treating team has the potential to enhance the timely recognition of sepsis. (14)

The current diagnostic model for sepsis relies predominately on objective tools, which pose numerous challenges due to the complex nature of paediatric physiology. (15) While the search for more precise biomarkers for sepsis continues, little is known in relation to utilising concern as a diagnostic tool to aid in earlier recognition. (16) In addition to parental concern, the gut feeling or intuition of healthcare professionals may contribute to the recognition of sepsis. (17) In the primary care setting, a gut feeling that "something was wrong" reported by clinicians was linked with a high specificity and positive likelihood ratio for serious bacterial infections. (18) The inclusion of parental and healthcare worker concern in the diagnostic model has the potential ability to improve specificity, thereby increasing sepsis recognition and earlier treatment.

It is hypothesised that the inclusion of parental and healthcare professional concern in the ED will improve diagnostic accuracy and early recognition of paediatric sepsis. The main objective of this study is to determine the diagnostic accuracy of concern levels in parents, doctors and nurses to recognise paediatric sepsis in a prospective multicentre observational study.

METHODS AND ANALYSIS

Study Design

This prospective multi-centre observational cohort study will use a cross-sectional survey tool designed to independently assess the level of concern of parents, nurses and doctors for children who present to the ED and are evaluated for sepsis. The planned duration for the project will be 12 months for recruitment with 6 months for data cleaning, analyses and write

up. This study has been designed to fulfil criteria for the diagnostic accuracy studies (STARD). (19)

Study setting

This study will be conducted across the dedicated paediatric EDs at two tertiary Australian hospitals: Queensland Children's Hospital (QCH), which receives approximately 6600 presentations each month, and Gold Coast University Hospital (GCUH), which receives approximately 2300 paediatric presentations each month.

Participants

Eligible participants will be children aged between 30 days to 18 years presenting to the ED and evaluated for sepsis via the institutional sepsis pathway and/or undergo blood culture sampling for suspected infection.

Study Criteria

Participants will be selected using the eligibility criteria outlined in table 1.

Inclusion criteria	Exclusion criteria
• Child aged 30 days to 18 years old • Presented to ED • Evaluated for sepsis on the sepsis pathway and/or having blood culture sampling • Survey completed during ED stay, aiming to be completed at time closest to triage presentation. • Parent/Care-giver attending with child, treating doctor and/or nurse available for survey	• Parents who do not speak English • Children with high suspicion of SARS-CoV-2 infection • Patients in clinical areas outside the ED such as Paediatric Intensive Care Unit

Table 1: Study inclusion and exclusion criteria

Test Methods:

The study surveys have been individually designed for parents, nurses and doctors, incorporating both quantitative and qualitative measures (Figure 1, Figure 2 and Figure 3). To ensure consistent comparison, all surveys have the same basic design and content, with the doctor and nurse surveys the same and minor adaptions on the parent/carer survey to reflect

the participant role (parent vs nurse/doctor). Participants are asked to rate the degree to which they agree or disagree with a statement or question using a 5-point Likert scale, (20) followed by two free text questions. This method of testing was chosen due to the advantage of the survey facilitating questions in a straightforward and simple manner, which will be pragmatic for respondents to use, a critical requirement for recruitment in an ED setting. The surveys were piloted 20 times to ensure questionnaire feasibility. Job title and years of experience for participating doctors and nurses will be collected. (17)

The surveys will be distributed to one of the child's parents/caregiver's, nurse and doctor on presentation and will be completed during ED stay. The distribution of these surveys will occur 7 days a week 27/4 through the ED staff supported from the dedicated research team. We aim for surveys to be completed at time closest to triage and within 4-hrs from initial presentation. This window for survey administration was determined based on the current Australian National Emergency Assess Target guidelines which stipulate that patients must be admitted, discharged or transferred from ED within 4 hours of initial presentation. (21) These surveys are embedded within the *Queensland Sepsis Pathway* which was developed and implemented across Queensland paediatric EDs.

Sample Size

A minimum of 400 patients will be recruited over the two sites. This minimum sample size was selected based on a sample size calculation which revealed that with an expected prevalence of 10% and an expected improvement in sensitivity from 0.6 to 0.8, a sample size of 450 is needed. (22)

Data Collection

The patient demographics, information regarding the presentation and illness severity at baseline will be collected from the medical record. In addition, the worst measure of physiological parameters and maximum level of support during the first 48 hours will be captured. Illness severity will be determined using the Paediatric Sequential Organ Failure Assessment (pSOFA) score. (23) Data will be recorded into a RedCap case report form.

Analysis Plan

Suspected or proven infection in presence of organ dysfunction, defined as a pSOFA score >0 at time of assessment, is defined as the primary outcome. Two secondary outcomes are defined: a) suspected or proven infection and development of organ dysfunction, defined as a pSOFA score >0, within 48hours of presentation; and b) confirmed or probable bacterial infection independent of organ dysfunction. The likelihood of bacterial versus viral infection will be assessed using all available laboratory, microbiological, and clinical information with adjudication of patients (24) into *confirmed bacterial infection* (positive microbiological cultures compatible with the clinical syndrome, and decision by the treating physician to treat for at least 5 days or until death with antibiotics), *probable bacterial infection* (negative microbiological cultures in presence of a clinical syndrome of bacterial infection and increased C-reactive protein, and decision by the treating physician to treat for at least 5 days or until death with antibiotics), *probable viral infection* (negative microbiological tests in presence of a clinical syndrome of viral infection such as bronchiolitis), *proven viral infection* (positive microbiological testing in presence of a clinical syndrome of viral infection), *infection of uncertain origin*, and *non-infectious conditions*.

Descriptive analyses will report on the demographics and baseline patient features, including hospital length of stay. Illness severity will be measured through the pSOFA score. Description on the level of completeness of the surveys (parental, nursing, medical) and patient characteristics will be provided and the differences in demographics will be investigated between children who have completed surveys from all three participant groups and those who have missing surveys.

First, an exploratory factor analysis will be performed on the questions used in the surveys to determine whether the questions are measuring the same latent construct, concern, or if more than one construct is present. In addition, the internal consistency and inter-rater reliability of the items will be assessed using Cronbach's alpha and Cohen`s kappa. Based on the results of the factor analysis, the questions which have the strongest factor loadings will be identified and included in the mixed effects model.

Next, a linear mixed effects model will be performed for the primary and secondary outcomes to assess the associations between the selected concern items and the outcome. A random intercept will be estimated for each child, to assess the variation in illness severity between children and a random slope for concern will also be explored for each child and

each participant group, to account for the different responders per child. Other demographic and comorbidities, which are predictors of sepsis, will be included in the model as control variables. The AUROC, sensitivity, specificity, negative and positive predictive value and likelihood ratios will be calculated to assess model fit and predictive performance.

P-values below 0.05 will be considered as significant and 95% confidence intervals will be reported alongside all significant effects. All analyses will be performed by an expert statistician using R. (25)

A pre-planned secondary analysis will assess qualitative data from the survey free text questions utilising the Framework Method (Gale et al., 2013). These free texts will then be examined and sorted into multiple categories to determine commonalities and differences. These categories will then be sorted into themes for the three groups: parents, doctors and nurses. Confirmation of these themes will be in collaboration with the research team to maintain rigor, validity and transparency of analysis. (26)

Strengths

A strength of this study is its prospective observational study design with a large multicentre cohort of children evaluated for sepsis. In contrast to previous studies which more broadly captured serious bacterial infections (18) or pyrexia, (27) the present study captures sepsis defined as suspected/proven infection with organ dysfunction as the main outcome. The study design enables assessment of the role of parental and healthcare professional concern in diagnosing paediatric sepsis and compares the respective diagnostic accuracies with the diagnostic performance of the routine diagnostic process.

This study aims to address an established gap regarding the significance of parental and healthcare professional concern in predicting disease severity in children with infection. Outcomes can inform the design of improved sepsis recognition tools. While the study will be conducted within the ED, findings relating to the use of concern as a red flag and a prompt for further investigation and assessment could be translated into other clinical settings.

Limitations

This study presents several limitations. It is expected that some patients will only have partial sets of surveys completed due to circumstances such as a parent being deemed unfit to

complete a research survey for various reasons, or the attending nurse or doctor not completing a survey. The incomplete sets of surveys for patients is anticipated given the pragmatic nature of the study and will be a consideration when conducting analysis and reporting. Bias could occur through children who are more clinically well having a greater number of concern surveys completed, as opposed to more clinically unwell children, whereby parents may be too distressed and healthcare professionals otherwise occupied treating the child. (28) Standardised dissemination of study education will aim to reduce potential bias related to variances on how the surveys are administered to parents, doctors and nurses. Implementation of an educational script will eliminate the use of words such as sepsis, organ dysfunction or death which may potentially heighten concern levels or result in changes to concern.

Finally, the study will be performed in two sites working within the same healthcare system in a high-income country, and, hence, similar studies in low and middle income settings will be required to assess generalisability.

Ethics and dissemination

Informed verbal consent will be gained from the parent/care-giver, nurse and doctor at the time of survey administration. It will be reiterated to all parties that they have the right to refuse participation at initial time of consent or withdraw at any stage without affecting patient care or their employment, as applicable. The survey and study design have been approved by the Children's Health Queensland Human Research Ethics Committee (HREC/17/QRCH/85).

Findings will be shared with relevant stakeholders and disseminated via conferences and peer-reviewed journals.

Patient and public involvement

Parents have not been involved in the design of the survey tool. However, key findings will be shared via the parent-consumer representatives during dissemination at a local and national level.

Contributors: LJS conceived the project and provided the technical and intellectual inputs supporting ZS and AH in writing this manuscript and approved it for submission. ZS produced the first draft and subsequent drafts of the paper. AH and ZS lead central coordination and contributed to the design of the analysis plan. ZS, LJS, MJ, SG, PG and AH

were involved in review and provided inputs on the manuscript. All authors reviewed and approved various drafts and the final paper.

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Competing interests None declared.

Figures
Figure 1: Parental survey
Figure 2: Nursing survey
Figure 3: Medical survey

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Study ID: .....

Date &Time: .....

(Affix patient identification label here)

URN:

Family Name:

Given Names:

Address:

Date of Birth: Sex: ☐ M ☐ F ☐ I

Parent/Care-Giver

RAPIDS Study

We would like to ask you to participate in this study. We are interested in measuring the parental concern as a tool to predict how severe a child's illness may be. No one knows your child better than you so we ask that you please complete this short survey to indicate if/what concerns you most about your child's illness. ***By completing this survey you are consenting to us analysing this data together with information from the medical health record for research purposes.***

1. Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your child's illness:

Not Concerned	1	2	3	4	5	Extremely Concerned

2. Do you have a gut feeling that something is wrong with your child? Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your child's illness:

I feel things are ok	1	2	3	4	5	I feel something is Extremely Wrong

3. Please place an 'X' in the below fields to indicate how different is your child's behaviour right now compared to normal?

Normal Behaviour for Child	1	2	3	4	5	Extremely Abnormal Behaviour for Child

4. What are the symptoms/behaviours that your child displayed, which prompted you to bring your child to hospital? *Please list as many as possible:*

1. ..... **3.** .....

2. ..... **4.** .....

5. What was the symptom that concerned you the most?

.....

6. Please place an 'X' in the below fields to indicate how severe you feel your child's illness is *today?*

Mildly Unwell	1	2	3	4	5	Severely Unwell

7. Please place an 'X' in the below fields to indicate how unwell you feel your child is today compared to *how unwell they have been in the past*:

Mild Illness for Child	1	2	3	4	5	Most Severe Illness for Child

Figure 1: Parental Survey

Study ID: .....

Date &Time: .....

(Affix patient identification label here)

URN:

Family Name:

Given Names:

Address:

Date of Birth: Sex: ☐ M ☐ F ☐ I

Nursing Survey

RAPIDS Trial

We would like to ask you to participate in this study. We are interested in measuring the treating nurse's level of concern as a tool to predict how severe a child's illness may be. We ask that you please complete this short survey to indicate what concerns you most about your patient's illness. By completing this survey you are consenting to us including this data for research purposes.

Job Title (RN/CN): .....

Years of Experience: .....

1. Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your patient's illness

Not Concerned	1	2	3	4	5	Extremely Concerned

2. Do you have a gut feeling that something is wrong with your patient? Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your child's illness:

I feel things are ok	1	2	3	4	5	I feel something is Extremely Wrong

3. Please place an 'X' in the below fields to indicate how different is your patient's behaviour deviating from their norm based on your discussion with patient/parent?

Normal Behaviour for Child	1	2	3	4	5	Extremely Abnormal Behaviour for Child

4. What are the symptoms/behaviours that your patient displayed that trigger your concern?
Please list as many as possible

1. ..... 3. .....

2. ..... 4. .....

5. What was the symptom that concerned you the most?

.....

6. Please place an 'X' in the below fields to indicate how severe you feel your patient's illness is:

Mildly Unwell	1	2	3	4	5	Severely Unwell

Figure 2: Nursing Survey

Study ID: .....

Date &Time: .....

Medical Survey

RAPIDS Trial

(Affix patient identification label here)

URN:

Family Name:

Given Names:

Address:

Date of Birth: Sex: ☐ M ☐ F ☐ I

We would like to ask you to participate in this study. We are interested in measuring the treating doctor's level of concern as a tool to predict how severe a child's illness may be. We ask that you please complete this short survey to indicate what concerns you most about your patient's illness. By completing this survey you are consenting to us including this data for research purposes.

Job Title (e.g. SMO): .....

Years of Experience: .....

1. Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your patient's illness

Not Concerned	1	2	3	4	5	Extremely Concerned

2. Do you have a gut feeling that something is wrong with your patient? Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your child's illness:

I feel things are ok	1	2	3	4	5	I feel something is Extremely Wrong

3. Please place an 'X' in the below fields to indicate how different is your patient's behaviour deviating from their norm based on your discussion with patient/parent?

Normal Behaviour for Child	1	2	3	4	5	Extremely Abnormal Behaviour for Child

4. What are the symptoms/behaviours that your patient displayed that trigger your concern?
Please list as many as possible

1. ..... 3. .....

2. ..... 4. .....

5. What was the symptom that concerned you the most?

.....

6. Please place an 'X' in the below fields to indicate how severe you feel your patient's illness is:

Mildly Unwell	1	2	3	4	5	Severely Unwell

Figure 3: Medical Survey

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	#1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	#1
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	#1
	4	Study objectives and hypotheses	#2
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	#2
Participants	**6**	Eligibility criteria	#3
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	#4
	8	Where and when potentially eligible participants were identified (setting, location and dates)	#2
	9	Whether participants formed a consecutive, random or convenience series	Not specified
Test methods	**10a**	Index test, in sufficient detail to allow replication	N/A
	10b	Reference standard, in sufficient detail to allow replication	N/A
	11	Rationale for choosing the reference standard (if alternatives exist)	N/A
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	#5
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	N/A
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	N/A
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	N/A
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	#5
	15	How indeterminate index test or reference standard results were handled	N/A
	16	How missing data on the index test and reference standard were handled	N/A
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	#5
	18	Intended sample size and how it was determined	#4
RESULTS			
Participants	**19**	Flow of participants, using a diagram	#3 (no diagram)
	20	Baseline demographic and clinical characteristics of participants	N/A
	21a	Distribution of severity of disease in those with the target condition	N/A
	21b	Distribution of alternative diagnoses in those without the target condition	N/A
	22	Time interval and any clinical interventions between index test and reference standard	N/A
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	N/A
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	#5
	25	Any adverse events from performing the index test or the reference standard	N/A
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	#6
	27	Implications for practice, including the intended use and clinical role of the index test	N/A
OTHER INFORMATION			
	28	Registration number and name of registry	#1
	29	Where the full study protocol can be accessed	Only submitted, not yet accessible

	30	Sources of funding and other support; role of funders	#7

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

BMJ Open

Parental and Healthcare Professional Concern in the Diagnosis of Paediatric Sepsis: A Protocol for a Prospective Multicentre Observational Study

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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Emergency medicine
Keywords:	Paediatric A&E and ambulatory care < PAEDIATRICS, Paediatric intensive & critical care < PAEDIATRICS, Paediatric infectious disease & immunisation < PAEDIATRICS

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TITLE

Parental and Healthcare Professional Concern in the Diagnosis of Paediatric Sepsis: A Protocol for a Prospective Multicentre Observational Study

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KEYWORDS: Sepsis; Paediatrics; Intuition; Emergency Service, Hospital; Infection

WORD COUNT: 2656

ABSTRACT

Introduction: Paediatric sepsis is a major contributor to morbidity and mortality worldwide. Assessing concern from parents and healthcare professionals to determine disease severity in a child evaluated for sepsis remains a field requiring further investigation. This study aims to determine the diagnostic accuracy of parental and healthcare professional concern in the diagnosis of children evaluated for sepsis.

Methods and analysis: This prospective multicentre observational study will be conducted over a 24-month period in paediatric Emergency Department (EDs) at two tertiary Australian hospitals. A cross-sectional survey design will be utilised to assess the level of concern of parents, nurses and doctors for children presenting to ED and assessed for sepsis. The primary outcome is diagnosis of sepsis defined as suspected infection plus organ dysfunction at time of survey completion. Secondary outcomes include suspected or proven infection and development of organ dysfunction, defined as a pSOFA score >0, within 48hours of presentation, Pediatric Intensive Care Unit admission and confirmed or probable bacterial infection independent of organ dysfunction.

Ethics and dissemination: Ethics approval was obtained from Children's Health XXX Human Research Ethics Committee (HREC/17/QRCH/XX).Findings will be shared with relevant stakeholders and disseminated via conferences and peer-reviewed journals.

Universal trial number: U1111-1256-4537

Keywords: Sepsis; Paediatrics; Children; Intuition; Emergency Service, Hospital; Infection

Strengths and limitations of this study:

- Prospective assessment of parental, nursing, and medical concern will be undertaken both quantitatively and qualitatively.
- Embedding the study in an established institutional paediatric sepsis pathway reduces barriers for staff engagement.
- Although this is the largest study on parental and healthcare professional concern in recognising paediatric sepsis, consideration for other sources of diagnostic bias as a result of referral, previous history, and concomitant interventions is required.

INTRODUCTION

Sepsis is a major contributor to morbidity and mortality in children worldwide. (1) The World Health Organization recently identified sepsis as a key health priority, outlining the high global burden of this time critical and often preventable disease. (2) While the latest definition of paediatric sepsis dates back to 2005, (3) the definition of sepsis in adults was re-defined in 2016 as 'life threatening organ dysfunction caused by a dysregulated host response to infection'. (4) Globally, close to 50 million patients suffer from sepsis each year, with over 10 million sepsis-related deaths, (5) the highest incidence affecting infants and children. While the highest burden related to sepsis affects low and middle income settings, sepsis remains amongst the leading causes of (potentially preventable) morbidity and mortality in high income countries too, accounting for a total cost of $7.31 billion dollars in the United States alone. (6) These high economic costs, along with the persistently high prevalence and morbidity of paediatric sepsis, highlight the urgent need for further research into earlier sepsis recognition.

Prompt identification is well recognised as fundamental for the early intervention and treatment of sepsis. In a large retrospective study of children with sepsis, the delay in the administration of a sepsis treatment bundle consisting of intravenous antibiotics, fluids and blood cultures was associated with a significant increase in mortality. (7) The majority of paediatric sepsis deaths occur within the first 48 hours of initial admission to the Intensive Care Unit, (8) emphasising the need for prompt recognition and resuscitation. The new Surviving Sepsis Guidelines (9) further emphasise the need for early detection, as it is a critical survival factor for paediatric sepsis, with timely and appropriate initiation of interventions being linked to improved patient outcomes.

Paediatric sepsis is an insidious condition which poses many challenges for healthcare professionals to accurately and timely diagnose. This is due to the vague and non-specific nature of the disease coupled with a relatively low incidence rate compared to the number of children presenting to the Emergency Department (ED) with febrile illness. (10) This low incidence of sepsis presents a challenge akin to finding a 'needle in a haystack' for clinicians. Consequently, the risk for a missed or misdiagnosis is high and subsequent repercussions are potentially lifelong and fatal. (11) In its early stages, sepsis often resembles many other common febrile illnesses with the clinical signs of fever, tachycardia and tachypnoea. (12)

Parents, as experts of their child, may be valuable in the identification of sepsis and discrimination of the condition as opposed to other milder illnesses.

Observational studies suggest that parents may recognise illness severity before nurses and doctors, independent of key clinical signs. (13) Root-cause-analyses and anecdotal data after fatal paediatric sepsis outcomes established that children often re-presented several times and parents commonly indicated concerns that the "illness was different". (13) A more holistic and family-centred-care approach incorporating collaboration between the child's family and treating team has the potential to enhance the timely recognition of sepsis. (14)

The current diagnostic model for sepsis relies predominately on objective tools, which pose numerous challenges due to the complex nature of paediatric physiology. (15) While the search for more precise biomarkers for sepsis continues, little is known in relation to utilising concern as a diagnostic tool to aid in earlier recognition. (16) In addition to parental concern, the gut feeling or intuition of healthcare professionals may contribute to the recognition of sepsis. (17) In the primary care setting, a gut feeling that "something was wrong" reported by clinicians was linked with a high specificity and positive likelihood ratio for serious bacterial infections. (18) The inclusion of parental and healthcare worker concern in the diagnostic model has the potential ability to improve specificity, thereby increasing sepsis recognition and earlier treatment.

It is hypothesised that the inclusion of parental and healthcare professional concern in the ED will improve diagnostic accuracy and early recognition of paediatric sepsis. The main objective of this study is to determine the diagnostic accuracy of concern levels in parents, doctors and nurses to recognise paediatric sepsis in a prospective multicentre observational study. New knowledge generated from the study may contribute to the earlier recognition and treatment of paediatric sepsis.

METHODS AND ANALYSIS

Study Design

This prospective multi-centre observational cohort study will use a cross-sectional survey tool designed to independently assess the level of concern of parents, nurses and doctors for children who present to the ED and are evaluated for sepsis. The planned duration for the

project will be 24 months for recruitment with 6 months for data cleaning, analyses and write up. More specifically, the study first recruited in December 2018 and last recruited in January 2021. This study has been designed to fulfil criteria for the diagnostic accuracy studies (STARD). (19)

Study setting

This study will be conducted across the dedicated paediatric EDs at two tertiary Australian hospitals: Queensland Children's Hospital (QCH), which receives approximately 6600 presentations each month, and Gold Coast University Hospital (GCUH), which receives approximately 2300 paediatric presentations each month.

Participants

Eligible participants will be children aged between 30 days to 18 years presenting to the ED and evaluated for sepsis via the institutional sepsis pathway and/or undergo blood culture sampling for suspected infection (Table 1).

Study Criteria

Inclusion criteria	Exclusion criteria
• Child aged 30 days to 18 years old • Presented to ED • Evaluated for sepsis on the sepsis pathway and/or having blood culture sampling • Survey completed during ED stay, aiming to be completed at time closest to triage presentation. • Parent/Care-giver attending with child, treating doctor and/or nurse available for survey	• Parents who do not speak English • Children with high suspicion of SARS-CoV-2 infection[i] • Patients in clinical areas outside the ED such as Paediatric Intensive Care Unit

Table 1: Study inclusion and exclusion criteria

i: Research governance did not permit researchers to risk exposure to SARS-CoV2 infection

Test Methods:

The study surveys have been individually designed for parents, nurses and doctors, incorporating both quantitative and qualitative measures (Figure 1, 2, 3). To ensure consistent

comparison, all surveys have the same basic design and content, with the doctor and nurse surveys the same and minor adaptions on the parent/carer survey to reflect the participant role (parent vs nurse/doctor). Participants are asked to rate the degree to which they agree or disagree with a statement or question using a 5-point Likert scale, (20) followed by two free text questions. This method of testing was chosen due to the advantage of the survey facilitating questions in a straightforward and simple manner, which will be pragmatic for respondents to use, a critical requirement for recruitment in an ED setting. The surveys were piloted 20 times to ensure questionnaire feasibility. Job title and years of experience for participating doctors and nurses will be collected. (17)

The surveys will be distributed to one of the child's parents/caregiver's, nurse and doctor on presentation and will be completed during ED stay. The distribution of these surveys will occur 7 days a week 24 hours a day through the ED staff with support from the dedicated research team. We aim for surveys to be completed at time closest to triage and within 4 hours from initial presentation. This window for survey administration was determined based on the current Australian National Emergency Assess Target guidelines which stipulate that patients must be admitted, discharged or transferred from ED within 4 hours of initial presentation. (21) These surveys are embedded within the *Queensland Sepsis Pathway* which was developed and implemented across Queensland paediatric EDs.

Sample Size

A minimum of 450 patients will be recruited over the two sites. This minimum sample size was selected based on a sample size calculation which revealed that with an expected prevalence of 10% and an expected improvement in sensitivity from 0.6 to 0.8, a sample size of 450 is needed. (22)

Data Collection

The patient demographics, information regarding the presentation and illness severity at baseline will be collected from the medical record. In addition, the worst measure of physiological parameters and maximum level of support during the first 48 hours will be captured. Illness severity will be determined using the Paediatric Sequential Organ Failure Assessment (pSOFA) score. (23) Data will be recorded into a RedCap case report form.

Analysis Plan

Suspected or proven infection in presence of organ dysfunction, defined as a pSOFA score >0 at time of assessment, is defined as the primary outcome. Given the ongoing controversy around paediatric sepsis definitions (12), sensitivity analyses with organ dysfunction defined as per the 2005 International Paediatric Definitions Consensus Conference will be performed. (3,24) Secondary outcomes are defined as: a) suspected or proven infection and development of organ dysfunction, defined as a pSOFA score >0, within 48hours of presentation; b) admission to the PICU; c) confirmed or probable bacterial infection independent of organ dysfunction; and d) hospital length of stay. The likelihood of bacterial versus viral infection will be determined by two independent assessors using all available laboratory, microbiological, and clinical information with adjudication of patients. (25) Bacterial infection will be categorised as *confirmed bacterial infection* (positive microbiological cultures compatible with the clinical syndrome, and decision by the treating physician to treat for at least 5 days or until death with antibiotics) or *probable bacterial infection* (negative microbiological cultures in presence of a clinical syndrome of bacterial infection and increased C-reactive protein, and decision by the treating physician to treat for at least 5 days or until death with antibiotics). Viral infection will be categorised as *probable viral infection* (negative microbiological tests in presence of a clinical syndrome of viral infection such as bronchiolitis) or *proven viral infection* (positive microbiological testing in presence of a clinical syndrome of viral infection). If the presentation is determined to be of non-infectious or unknown origin, it will be classed as *infection of uncertain origin*, and *non-infectious conditions*.

Descriptive analyses will report on the demographics and baseline patient features. Description on the level of completeness of the surveys (parental, nursing, medical) will be provided and any differences in demographics will be investigated between children who have completed surveys from all three participant groups and those who have missing surveys.

To assess the relationship between the concern ratings and outcome, firstly an exploratory factor analysis will be performed on the four concern questions assessed in the surveys to determine whether the questions are measuring the same latent construct ("concern") or if more than one construct is present. In addition, the internal consistency and inter-rater

reliability of the concern questions will be assessed using Cronbach's alpha and the intraclass correlation using a one-way random effects model, respectively. Based on the results of the factor analysis a factor score will be created and used as a measure of concern in the regression models. In addition, the relationship between the four individual concern questions with the primary outcome will be assessed through bivariate logistic regression models. The question that provides the best prediction of sepsis will be identified as the one that has the highest unadjusted odds ratio and area under the receiver operating characteristic curve (AUROC), with 95% confidence intervals (CIs) being reported alongside all effects.

Next, regression models will be derived for the primary and secondary outcomes to assess the associations between the concern factor score and the "best" concern question with the outcome. Other demographic characteristics and physiological variables, which are associated with the outcomes of interest, will be included in the model as control variables. The AUROC, sensitivity, specificity, negative and positive likelihood ratios (along with associated 95% CIs) will be calculated to assess model fit and predictive performance.

All regression modelling will be performed on each of the three responder cohorts separately (i.e., children with a parental survey, children with a nurse survey and children with a medical survey completed) to identify whether the effect of concern on the outcomes is dependent on the responder. P-values below 0.05 will be considered as statistically significant. All analyses will be performed by an expert statistician using R. (26)

A pre-planned secondary analysis will assess qualitative data from the survey free text questions utilising the Framework Method. (27) These free texts will then be examined and sorted into multiple categories to determine commonalities and differences. These categories will then be sorted into themes for the three groups: parents, doctors and nurses. Confirmation of these themes will be in collaboration with the research team to maintain rigor, validity and transparency of analysis. (27)

Strengths

A strength of this study is its prospective observational study design with a large multicentre cohort of children evaluated for sepsis. In contrast to previous studies which more broadly captured serious bacterial infections (18) or pyrexia, (28) the present study captures sepsis defined as suspected/proven infection with organ dysfunction as the main outcome. The study

design enables assessment of the role of parental and healthcare professional concern in diagnosing paediatric sepsis and compares the respective diagnostic accuracies with the diagnostic performance of the routine diagnostic process.

This study aims to address an established gap regarding the significance of parental and healthcare professional concern in predicting disease severity in children with infection. Outcomes can inform the design of improved sepsis recognition tools. While the study will be conducted within the ED, findings relating to the use of concern as a red flag and a prompt for further investigation and assessment could be translated into other clinical settings.

Limitations

This study presents several limitations. It is expected that some patients will only have partial sets of surveys completed due to circumstances such as a parent being deemed unfit to complete a research survey for various reasons, or the attending nurse or doctor not completing a survey. The incomplete sets of surveys for patients are anticipated given the pragmatic nature of the study and will be a consideration when conducting analysis and reporting. Bias could occur through children who are more clinically well having a greater number of concern surveys completed, as opposed to more clinically unwell children, whereby parents may be too distressed and healthcare professionals otherwise occupied treating the child (29). Standardised dissemination of study education will aim to reduce potential bias related to variances on how the surveys are administered to parents, doctors and nurses. Implementation of an educational script will eliminate the use of words such as sepsis, organ dysfunction or death which may potentially heighten concern levels or result in changes to concern. Finally, the study will be performed in two sites working within the same healthcare system in a high-income country, and, hence, similar studies in low and middle income settings will be required to assess generalisability.

Ethics and dissemination

Informed verbal consent will be gained from the parent/care-giver, nurse and doctor at the time of survey administration. It will be reiterated to all parties that they have the right to refuse participation at initial time of consent or withdraw at any stage without affecting patient care or their employment, as applicable. The survey and study design have been approved by the Children's Health Queensland Human Research Ethics Committee (HREC/17/QRCH/85).

Findings will be shared with relevant stakeholders and disseminated via conferences and peer-reviewed journals.

Patient and public involvement

Parents have not been involved in the design of the survey tool. However, key findings will be shared via the parent-consumer representatives during dissemination at a local and national level.

Contributors: LJS conceived the project and provided the technical and intellectual inputs supporting ZS and AH in writing this manuscript and approved it for submission. ZS produced the first draft and subsequent drafts of the paper. AH and ZS lead central coordination and contributed to the design of the analysis plan. ZS, LJS, MJ, SG and AH were involved in review and provided inputs on the manuscript. All authors reviewed and approved various drafts and the final paper.

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Competing interests None declared.

Figures

Figure 1: Parental survey

Figure 2: Nursing survey

Figure 3: Medical survey

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Study ID: .....

Date &Time: .....

(Affix patient identification label here)

URN:

Family Name:

Given Names:

Address:

Date of Birth: Sex: ☐ M ☐ F ☐ I

Parent/Care-Giver

RAPIDS Study

We would like to ask you to participate in this study. We are interested in measuring the parental concern as a tool to predict how severe a child's illness may be. No one knows your child better than you so we ask that you please complete this short survey to indicate if/what concerns you most about your child's illness. ***By completing this survey you are consenting to us analysing this data together with information from the medical health record for research purposes.***

1. Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your child's illness:

Not Concerned	1	2	3	4	5	Extremely Concerned

2. Do you have a gut feeling that something is wrong with your child? Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your child's illness:

I feel things are ok	1	2	3	4	5	I feel something is Extremely Wrong

3. Please place an 'X' in the below fields to indicate how different is your child's behaviour right now compared to normal?

Normal Behaviour for Child	1	2	3	4	5	Extremely Abnormal Behaviour for Child

4. What are the symptoms/behaviours that your child displayed, which prompted you to bring your child to hospital? *Please list as many as possible:*

1. ..... **3.** .....

2. ..... **4.** .....

5. What was the symptom that concerned you the most?

.....

6. Please place an 'X' in the below fields to indicate how severe you feel your child's illness is *today?*

Mildly Unwell	1	2	3	4	5	Severely Unwell

7. Please place an 'X' in the below fields to indicate how unwell you feel your child is today compared to *how unwell they have been in the past*:

Mild Illness for Child	1	2	3	4	5	Most Severe Illness for Child

Figure 1: Parental Survey

Study ID: .....

Date &Time: .....

(Affix patient identification label here)

URN:

Family Name:

Given Names:

Address:

Date of Birth: Sex: ☐ M ☐ F ☐ I

Nursing Survey

RAPIDS Trial

We would like to ask you to participate in this study. We are interested in measuring the treating nurse's level of concern as a tool to predict how severe a child's illness may be. We ask that you please complete this short survey to indicate what concerns you most about your patient's illness. By completing this survey you are consenting to us including this data for research purposes.

Job Title (RN/CN): .....

Years of Experience: .....

1. Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your patient's illness

Not Concerned	1	2	3	4	5	Extremely Concerned

2. Do you have a gut feeling that something is wrong with your patient? Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your child's illness:

I feel things are ok	1	2	3	4	5	I feel something is Extremely Wrong

3. Please place an 'X' in the below fields to indicate how different is your patient's behaviour deviating from their norm based on your discussion with patient/parent?

Normal Behaviour for Child	1	2	3	4	5	Extremely Abnormal Behaviour for Child

4. What are the symptoms/behaviours that your patient displayed that trigger your concern?
Please list as many as possible

1. ..... 3. .....

2. ..... 4. .....

5. What was the symptom that concerned you the most?

.....

6. Please place an 'X' in the below fields to indicate how severe you feel your patient's illness is:

Mildly Unwell	1	2	3	4	5	Severely Unwell

Figure 2: Nursing Survey

Study ID: .....

Date &Time: .....

Medical Survey

RAPIDS Trial

(Affix patient identification label here)

URN:

Family Name:

Given Names:

Address:

Date of Birth: Sex: ☐ M ☐ F ☐ I

We would like to ask you to participate in this study. We are interested in measuring the treating doctor's level of concern as a tool to predict how severe a child's illness may be. We ask that you please complete this short survey to indicate what concerns you most about your patient's illness. By completing this survey you are consenting to us including this data for research purposes.

Job Title (e.g. SMO): .....

Years of Experience: .....

1. Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your patient's illness

Not Concerned	1	2	3	4	5	Extremely Concerned

2. Do you have a gut feeling that something is wrong with your patient? Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your child's illness:

I feel things are ok	1	2	3	4	5	I feel something is Extremely Wrong

3. Please place an 'X' in the below fields to indicate how different is your patient's behaviour deviating from their norm based on your discussion with patient/parent?

Normal Behaviour for Child	1	2	3	4	5	Extremely Abnormal Behaviour for Child

4. What are the symptoms/behaviours that your patient displayed that trigger your concern?
Please list as many as possible

1. ..... 3. .....

2. ..... 4. .....

5. What was the symptom that concerned you the most?

.....

6. Please place an 'X' in the below fields to indicate how severe you feel your patient's illness is:

Mildly Unwell	1	2	3	4	5	Severely Unwell

Figure 3: Medical Survey

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	#1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	#1
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	#1
	4	Study objectives and hypotheses	#2
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	#2
Participants	**6**	Eligibility criteria	#3
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	#4
	8	Where and when potentially eligible participants were identified (setting, location and dates)	#2
	9	Whether participants formed a consecutive, random or convenience series	Not specified
Test methods	**10a**	Index test, in sufficient detail to allow replication	N/A
	10b	Reference standard, in sufficient detail to allow replication	N/A
	11	Rationale for choosing the reference standard (if alternatives exist)	N/A
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	#5
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	N/A
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	N/A
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	N/A
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	#5
	15	How indeterminate index test or reference standard results were handled	N/A
	16	How missing data on the index test and reference standard were handled	N/A
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	#5
	18	Intended sample size and how it was determined	#4
RESULTS			
Participants	**19**	Flow of participants, using a diagram	#3 (no diagram)
	20	Baseline demographic and clinical characteristics of participants	N/A
	21a	Distribution of severity of disease in those with the target condition	N/A
	21b	Distribution of alternative diagnoses in those without the target condition	N/A
	22	Time interval and any clinical interventions between index test and reference standard	N/A
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	N/A
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	#5
	25	Any adverse events from performing the index test or the reference standard	N/A
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	#6
	27	Implications for practice, including the intended use and clinical role of the index test	N/A
OTHER INFORMATION			
	28	Registration number and name of registry	#1
	29	Where the full study protocol can be accessed	Only submitted, not yet accessible

	30	Sources of funding and other support; role of funders	#7

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

BMJ Open

Parental and Healthcare Professional Concern in the Diagnosis of Paediatric Sepsis: A Protocol for a Prospective Multicentre Observational Study

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Keywords:	Paediatric A&E and ambulatory care < PAEDIATRICS, Paediatric intensive & critical care < PAEDIATRICS, Paediatric infectious disease & immunisation < PAEDIATRICS

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TITLE

Parental and Healthcare Professional Concern in the Diagnosis of Paediatric Sepsis: A Protocol for a Prospective Multicentre Observational Study

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KEYWORDS: Sepsis; Paediatrics; Intuition; Emergency Service, Hospital; Infection

WORD COUNT: 2656

ABSTRACT

Introduction: Paediatric sepsis is a major contributor to morbidity and mortality worldwide. Assessing concern from parents and healthcare professionals to determine disease severity in a child evaluated for sepsis remains a field requiring further investigation. This study aims to determine the diagnostic accuracy of parental and healthcare professional concern in the diagnosis of children evaluated for sepsis.

Methods and analysis: This prospective multicentre observational study will be conducted over a 24-month period in paediatric Emergency Department (EDs) at two tertiary Australian hospitals. A cross-sectional survey design will be utilised to assess the level of concern of parents, nurses and doctors for children presenting to ED and assessed for sepsis. The primary outcome is diagnosis of sepsis defined as suspected infection plus organ dysfunction at time of survey completion. Secondary outcomes include suspected or proven infection and development of organ dysfunction, defined as a pSOFA score >0, within 48hours of presentation, Paediatric Intensive Care Unit admission and confirmed or probable bacterial infection independent of organ dysfunction.

Ethics and dissemination: Ethics approval was obtained from Children's Health Queensland Human Research Ethics Committee (HREC/17/QRCH/85). Findings will be shared with relevant stakeholders and disseminated via conferences and peer-reviewed journals.

Universal trial number: U1111-1256-4537

Keywords: Sepsis; Paediatrics; Children; Intuition; Emergency Service, Hospital; Infection

Strengths and limitations of this study:

- Prospective assessment of parental, nursing, and medical concern will be undertaken both quantitatively and qualitatively.
- Embedding the study in an established institutional paediatric sepsis pathway reduces barriers for staff engagement.
- Although this is the largest study on parental and healthcare professional concern in recognising paediatric sepsis, consideration for other sources of diagnostic bias as a result of referral, previous history, and concomitant interventions is required.

INTRODUCTION

Sepsis is a major contributor to morbidity and mortality in children worldwide. (1) The World Health Organization recently identified sepsis as a key health priority, outlining the high global burden of this time critical and often preventable disease. (2) While the latest definition of paediatric sepsis dates back to 2005, (3) the definition of sepsis in adults was re-defined in 2016 as 'life threatening organ dysfunction caused by a dysregulated host response to infection'. (4) Globally, close to 50 million patients suffer from sepsis each year, with over 10 million sepsis-related deaths, (5) the highest incidence affecting infants and children. While the highest burden related to sepsis affects low and middle income settings, sepsis remains amongst the leading causes of (potentially preventable) morbidity and mortality in high income countries too, accounting for a total cost of $7.31 billion dollars in the United States alone. (6) These high economic costs, along with the persistently high prevalence and morbidity of paediatric sepsis, highlight the urgent need for further research into earlier sepsis recognition.

Prompt identification is well recognised as fundamental for the early intervention and treatment of sepsis. In a large retrospective study of children with sepsis, the delay in the administration of a sepsis treatment bundle consisting of intravenous antibiotics, fluids and blood cultures was associated with a significant increase in mortality. (7) The majority of paediatric sepsis deaths occur within the first 48 hours of initial admission to the Intensive Care Unit, (8) emphasising the need for prompt recognition and resuscitation. The new Surviving Sepsis Guidelines (9) further emphasise the need for early detection, as it is a critical survival factor for paediatric sepsis, with timely and appropriate initiation of interventions being linked to improved patient outcomes.

Paediatric sepsis is an insidious condition which poses many challenges for healthcare professionals to accurately and timely diagnose. This is due to the vague and non-specific nature of the disease coupled with a relatively low incidence rate compared to the number of children presenting to the Emergency Department (ED) with febrile illness. (10) This low incidence of sepsis presents a challenge akin to finding a 'needle in a haystack' for clinicians. Consequently, the risk for a missed or misdiagnosis is high and subsequent repercussions are potentially lifelong and fatal. (11) In its early stages, sepsis often resembles many other common febrile illnesses with the clinical signs of fever, tachycardia and tachypnoea. (12)

Parents, as experts of their child, may be valuable in the identification of sepsis and discrimination of the condition as opposed to other milder illnesses.

Observational studies suggest that parents may recognise illness severity before nurses and doctors, independent of key clinical signs. (13) Root-cause-analyses and anecdotal data after fatal paediatric sepsis outcomes established that children often re-presented several times and parents commonly indicated concerns that the "illness was different". (13) A more holistic and family-centred-care approach incorporating collaboration between the child's family and treating team has the potential to enhance the timely recognition of sepsis. (14)

The current diagnostic model for sepsis relies predominately on objective tools, which pose numerous challenges due to the complex nature of paediatric physiology. (15) While the search for more precise biomarkers for sepsis continues, little is known in relation to utilising concern as a diagnostic tool to aid in earlier recognition. (16) In addition to parental concern, the gut feeling or intuition of healthcare professionals may contribute to the recognition of sepsis. (17) In the primary care setting, a gut feeling that "something was wrong" reported by clinicians was linked with a high specificity and positive likelihood ratio for serious bacterial infections. (18) The inclusion of parental and healthcare worker concern in the diagnostic model has the potential ability to improve specificity, thereby increasing sepsis recognition and earlier treatment.

It is hypothesised that the inclusion of parental and healthcare professional concern in the ED will improve diagnostic accuracy and early recognition of paediatric sepsis. The main objective of this study is to determine the diagnostic accuracy of concern levels in parents, doctors and nurses to recognise paediatric sepsis in a prospective multicentre observational study. New knowledge generated from the study may contribute to the earlier recognition and treatment of paediatric sepsis.

METHODS AND ANALYSIS

Study Design

This prospective multi-centre observational cohort study will use a cross-sectional survey tool designed to independently assess the level of concern of parents, nurses and doctors for children who present to the ED and are evaluated for sepsis. The planned duration for the

project will be 24 months for recruitment with 6 months for data cleaning, analyses and write up. More specifically, the study first recruited in December 2018 and last recruited in January 2021. This study has been designed to fulfil criteria for the diagnostic accuracy studies (STARD). (19)

Study setting

This study will be conducted across the dedicated paediatric EDs at two tertiary Australian hospitals: Queensland Children's Hospital (QCH), which receives approximately 6600 presentations each month, and Gold Coast University Hospital (GCUH), which receives approximately 2300 paediatric presentations each month.

Participants

Eligible participants will be children aged between 30 days to 18 years presenting to the ED and evaluated for sepsis via the institutional sepsis pathway and/or undergo blood culture sampling for suspected infection (Table 1).

Study Criteria

Inclusion criteria	Exclusion criteria
• Child aged 30 days to 18 years old • Presented to ED • Evaluated for sepsis on the sepsis pathway and/or having blood culture sampling • Survey completed during ED stay, aiming to be completed at time closest to triage presentation. • Parent/Care-giver attending with child, treating doctor and/or nurse available for survey	• Parents who do not speak English • Children with high suspicion of SARS-CoV-2 infection[i] • Patients in clinical areas outside the ED such as Paediatric Intensive Care Unit

Table 1: Study inclusion and exclusion criteria

i: Research governance did not permit researchers to risk exposure to SARS-CoV2 infection

Test Methods:

The study surveys have been individually designed for parents, nurses and doctors, incorporating both quantitative and qualitative measures (Figure 1, 2, 3). To ensure consistent

comparison, all surveys have the same basic design and content, with the doctor and nurse surveys the same and minor adaptions on the parent/carer survey to reflect the participant role (parent vs nurse/doctor). Participants are asked to rate the degree to which they agree or disagree with a statement or question using a 5-point Likert scale, (20) followed by two free text questions. This method of testing was chosen due to the advantage of the survey facilitating questions in a straightforward and simple manner, which will be pragmatic for respondents to use, a critical requirement for recruitment in an ED setting. The surveys were piloted 20 times to ensure questionnaire feasibility. Job title and years of experience for participating doctors and nurses will be collected. (17)

The surveys will be distributed to one of the child's parents/caregiver's, nurse and doctor on presentation and will be completed during ED stay. The distribution of these surveys will occur 7 days a week 24 hours a day through the ED staff with support from the dedicated research team. We aim for surveys to be completed at time closest to triage and within 4 hours from initial presentation. This window for survey administration was determined based on the current Australian National Emergency Assess Target guidelines which stipulate that patients must be admitted, discharged or transferred from ED within 4 hours of initial presentation. (21) These surveys are embedded within the *Queensland Sepsis Pathway* which was developed and implemented across Queensland paediatric EDs.

Sample Size

A minimum of 450 patients will be recruited over the two sites. This minimum sample size was selected based on a sample size calculation which revealed that with an expected prevalence of 10% and an expected improvement in sensitivity from 0.6 to 0.8, a sample size of 450 is needed. (22)

Data Collection

The patient demographics, information regarding the presentation and illness severity at baseline will be collected from the medical record. In addition, the worst measure of physiological parameters and maximum level of support during the first 48 hours will be captured. Illness severity will be determined using the Paediatric Sequential Organ Failure Assessment (pSOFA) score. (23) Data will be recorded into a RedCap case report form.

Analysis Plan

Suspected or proven infection in presence of organ dysfunction, defined as a pSOFA score >0 at time of assessment, is defined as the primary outcome. Given the ongoing controversy around paediatric sepsis definitions (12), sensitivity analyses with organ dysfunction defined as per the 2005 International Paediatric Definitions Consensus Conference will be performed. (3,24) Secondary outcomes are defined as: a) suspected or proven infection and development of organ dysfunction, defined as a pSOFA score >0, within 48hours of presentation; b) admission to the PICU; c) confirmed or probable bacterial infection independent of organ dysfunction; and d) hospital length of stay. The likelihood of bacterial versus viral infection will be determined by two independent assessors using all available laboratory, microbiological, and clinical information with adjudication of patients. (25) Bacterial infection will be categorised as *confirmed bacterial infection* (positive microbiological cultures compatible with the clinical syndrome, and decision by the treating physician to treat for at least 5 days or until death with antibiotics) or *probable bacterial infection* (negative microbiological cultures in presence of a clinical syndrome of bacterial infection and increased C-reactive protein, and decision by the treating physician to treat for at least 5 days or until death with antibiotics). Viral infection will be categorised as *probable viral infection* (negative microbiological tests in presence of a clinical syndrome of viral infection such as bronchiolitis) or *proven viral infection* (positive microbiological testing in presence of a clinical syndrome of viral infection). If the presentation is determined to be of non-infectious or unknown origin, it will be classed as *infection of uncertain origin*, and *non-infectious conditions*.

Descriptive analyses will report on the demographics and baseline patient features. Description on the level of completeness of the surveys (parental, nursing, medical) will be provided and any differences in demographics will be investigated between children who have completed surveys from all three participant groups and those who have missing surveys.

To assess the relationship between the concern ratings and outcome, firstly an exploratory factor analysis will be performed on the four concern questions assessed in the surveys to determine whether the questions are measuring the same latent construct ("concern") or if more than one construct is present. In addition, the internal consistency and inter-rater

reliability of the concern questions will be assessed using Cronbach's alpha and the intraclass correlation using a one-way random effects model, respectively. Based on the results of the factor analysis a factor score will be created and used as a measure of concern in the regression models. In addition, the relationship between the four individual concern questions with the primary outcome will be assessed through bivariate logistic regression models. The question that provides the best prediction of sepsis will be identified as the one that has the highest unadjusted odds ratio and area under the receiver operating characteristic curve (AUROC), with 95% confidence intervals (CIs) being reported alongside all effects.

Next, regression models will be derived for the primary and secondary outcomes to assess the associations between the concern factor score and the "best" concern question with the outcome. Other demographic characteristics and physiological variables, which are associated with the outcomes of interest, will be included in the model as control variables. The AUROC, sensitivity, specificity, negative and positive likelihood ratios (along with associated 95% CIs) will be calculated to assess model fit and predictive performance.

All regression modelling will be performed on each of the three responder cohorts separately (i.e., children with a parental survey, children with a nurse survey and children with a medical survey completed) to identify whether the effect of concern on the outcomes is dependent on the responder. P-values below 0.05 will be considered as statistically significant. All analyses will be performed by an expert statistician using R. (26)

A pre-planned secondary analysis will assess qualitative data from the survey free text questions utilising the Framework Method. (27) These free texts will then be examined and sorted into multiple categories to determine commonalities and differences. These categories will then be sorted into themes for the three groups: parents, doctors and nurses. Confirmation of these themes will be in collaboration with the research team to maintain rigor, validity and transparency of analysis. (27)

Strengths

A strength of this study is its prospective observational study design with a large multicentre cohort of children evaluated for sepsis. In contrast to previous studies which more broadly captured serious bacterial infections (18) or pyrexia, (28) the present study captures sepsis defined as suspected/proven infection with organ dysfunction as the main outcome. The study

design enables assessment of the role of parental and healthcare professional concern in diagnosing paediatric sepsis and compares the respective diagnostic accuracies with the diagnostic performance of the routine diagnostic process.

This study aims to address an established gap regarding the significance of parental and healthcare professional concern in predicting disease severity in children with infection. Outcomes can inform the design of improved sepsis recognition tools. While the study will be conducted within the ED, findings relating to the use of concern as a red flag and a prompt for further investigation and assessment could be translated into other clinical settings.

Limitations

This study presents several limitations. It is expected that some patients will only have partial sets of surveys completed due to circumstances such as a parent being deemed unfit to complete a research survey for various reasons, or the attending nurse or doctor not completing a survey. The incomplete sets of surveys for patients are anticipated given the pragmatic nature of the study and will be a consideration when conducting analysis and reporting. Bias could occur through children who are more clinically well having a greater number of concern surveys completed, as opposed to more clinically unwell children, whereby parents may be too distressed and healthcare professionals otherwise occupied treating the child (29). Standardised dissemination of study education will aim to reduce potential bias related to variances on how the surveys are administered to parents, doctors and nurses. Implementation of an educational script will eliminate the use of words such as sepsis, organ dysfunction or death which may potentially heighten concern levels or result in changes to concern. Finally, the study will be performed in two sites working within the same healthcare system in a high-income country, and, hence, similar studies in low and middle income settings will be required to assess generalisability.

Ethics and dissemination

Informed verbal consent will be gained from the parent/care-giver, nurse and doctor at the time of survey administration. It will be reiterated to all parties that they have the right to refuse participation at initial time of consent or withdraw at any stage without affecting patient care or their employment, as applicable. The survey and study design have been approved by the Children's Health Queensland Human Research Ethics Committee (HREC/17/QRCH/85).

Findings will be shared with relevant stakeholders and disseminated via conferences and peer-reviewed journals.

Patient and public involvement

Parents have not been involved in the design of the survey tool. However, key findings will be shared via the parent-consumer representatives during dissemination at a local and national level.

Contributors: LJS conceived the project and provided the technical and intellectual inputs supporting ZS and AH in writing this manuscript and approved it for submission. ZS produced the first draft and subsequent drafts of the paper. AH and ZS lead central coordination and contributed to the design of the analysis plan. ZS, LJS, MJ, SG and AH were involved in review and provided inputs on the manuscript. All authors reviewed and approved various drafts and the final paper.

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Competing interests None declared.

Figures

Figure 1: Parental survey

Figure 2: Nursing survey

Figure 3: Medical survey

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Study ID: .....

Date &Time: .....

(Affix patient identification label here)

URN:

Family Name:

Given Names:

Address:

Date of Birth: Sex: ☐ M ☐ F ☐ I

Parent/Care-Giver

RAPIDS Study

We would like to ask you to participate in this study. We are interested in measuring the parental concern as a tool to predict how severe a child's illness may be. No one knows your child better than you so we ask that you please complete this short survey to indicate if/what concerns you most about your child's illness. ***By completing this survey you are consenting to us analysing this data together with information from the medical health record for research purposes.***

1. Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your child's illness:

Not Concerned	1	2	3	4	5	Extremely Concerned

2. Do you have a gut feeling that something is wrong with your child? Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your child's illness:

I feel things are ok	1	2	3	4	5	I feel something is Extremely Wrong

3. Please place an 'X' in the below fields to indicate how different is your child's behaviour right now compared to normal?

Normal Behaviour for Child	1	2	3	4	5	Extremely Abnormal Behaviour for Child

4. What are the symptoms/behaviours that your child displayed, which prompted you to bring your child to hospital? *Please list as many as possible:*

1. ..... **3.** .....

2. ..... **4.** .....

5. What was the symptom that concerned you the most?

.....

6. Please place an 'X' in the below fields to indicate how severe you feel your child's illness is *today?*

Mildly Unwell	1	2	3	4	5	Severely Unwell

7. Please place an 'X' in the below fields to indicate how unwell you feel your child is today compared to *how unwell they have been in the past*:

Mild Illness for Child	1	2	3	4	5	Most Severe Illness for Child

Figure 1: Parental Survey

Study ID: .....

Date &Time: .....

(Affix patient identification label here)

URN:

Family Name:

Given Names:

Address:

Date of Birth: Sex: ☐ M ☐ F ☐ I

Nursing Survey

RAPIDS Trial

We would like to ask you to participate in this study. We are interested in measuring the treating nurse's level of concern as a tool to predict how severe a child's illness may be. We ask that you please complete this short survey to indicate what concerns you most about your patient's illness. By completing this survey you are consenting to us including this data for research purposes.

Job Title (RN/CN): .....

Years of Experience: .....

1. Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your patient's illness

Not Concerned	1	2	3	4	5	Extremely Concerned

2. Do you have a gut feeling that something is wrong with your patient? Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your child's illness:

I feel things are ok	1	2	3	4	5	I feel something is Extremely Wrong

3. Please place an 'X' in the below fields to indicate how different is your patient's behaviour deviating from their norm based on your discussion with patient/parent?

Normal Behaviour for Child	1	2	3	4	5	Extremely Abnormal Behaviour for Child

4. What are the symptoms/behaviours that your patient displayed that trigger your concern?
Please list as many as possible

1. ..... 3. .....

2. ..... 4. .....

5. What was the symptom that concerned you the most?

.....

6. Please place an 'X' in the below fields to indicate how severe you feel your patient's illness is:

Mildly Unwell	1	2	3	4	5	Severely Unwell

Figure 2: Nursing Survey

Study ID: .....

Date &Time: .....

Medical Survey

RAPIDS Trial

(Affix patient identification label here)

URN:

Family Name:

Given Names:

Address:

Date of Birth: Sex: ☐ M ☐ F ☐ I

We would like to ask you to participate in this study. We are interested in measuring the treating doctor's level of concern as a tool to predict how severe a child's illness may be. We ask that you please complete this short survey to indicate what concerns you most about your patient's illness. By completing this survey you are consenting to us including this data for research purposes.

Job Title (e.g. SMO): .....

Years of Experience: .....

1. Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your patient's illness

Not Concerned	1	2	3	4	5	Extremely Concerned

2. Do you have a gut feeling that something is wrong with your patient? Please place an 'X' in the below fields to indicate your current level of concern regarding the severity of your child's illness:

I feel things are ok	1	2	3	4	5	I feel something is Extremely Wrong

3. Please place an 'X' in the below fields to indicate how different is your patient's behaviour deviating from their norm based on your discussion with patient/parent?

Normal Behaviour for Child	1	2	3	4	5	Extremely Abnormal Behaviour for Child

4. What are the symptoms/behaviours that your patient displayed that trigger your concern?
Please list as many as possible

1. ..... 3. .....

2. ..... 4. .....

5. What was the symptom that concerned you the most?

.....

6. Please place an 'X' in the below fields to indicate how severe you feel your patient's illness is:

Mildly Unwell	1	2	3	4	5	Severely Unwell

Figure 3: Medical Survey

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	#1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	#1
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	#1
	4	Study objectives and hypotheses	#2
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	#2
Participants	**6**	Eligibility criteria	#3
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	#4
	8	Where and when potentially eligible participants were identified (setting, location and dates)	#2
	9	Whether participants formed a consecutive, random or convenience series	Not specified
Test methods	**10a**	Index test, in sufficient detail to allow replication	N/A
	10b	Reference standard, in sufficient detail to allow replication	N/A
	11	Rationale for choosing the reference standard (if alternatives exist)	N/A
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	#5
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	N/A
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	N/A
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	N/A
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	#5
	15	How indeterminate index test or reference standard results were handled	N/A
	16	How missing data on the index test and reference standard were handled	N/A
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	#5
	18	Intended sample size and how it was determined	#4
RESULTS			
Participants	**19**	Flow of participants, using a diagram	#3 (no diagram)
	20	Baseline demographic and clinical characteristics of participants	N/A
	21a	Distribution of severity of disease in those with the target condition	N/A
	21b	Distribution of alternative diagnoses in those without the target condition	N/A
	22	Time interval and any clinical interventions between index test and reference standard	N/A
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	N/A
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	#5
	25	Any adverse events from performing the index test or the reference standard	N/A
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	#6
	27	Implications for practice, including the intended use and clinical role of the index test	N/A
OTHER INFORMATION			
	28	Registration number and name of registry	#1
	29	Where the full study protocol can be accessed	Only submitted, not yet accessible

	30	Sources of funding and other support; role of funders	#7

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.