Long-term outcomes after paediatric sepsis (LOTUS)–A protocol for an Australian cohort study

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STUDY PROTOCOLS

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Long-term outcomes after paediatric sepsis (LOTUS)–A protocol for an Australian cohort study

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Abstract

Background: Globally, sepsis has been identified as one of the leading causes of preventable childhood mortality and morbidity. Previous studies on intensive care patients estimated that approximately 30% of children with sepsis experience some form of disability at discharge. Development of care has seen growing numbers of children treated for sepsis not requiring a PICU admission; however, outcomes in this population are yet to be understood. Further focus is required to understand sepsis survivorship across the wider population to address knowledge gaps and morbidity burden in the broader surviving population.

Aims: To assess the cognitive, physical, emotional and social health of children surviving sepsis 2 years after hospital discharge.

Study Design: A prospective, observational cohort study.

Results: Two hundred and thirty-two children will be screened, 2 years after their hospital admission, and approached for participation in this study. Children who are <18 years of age at follow-up, treated for sepsis-related organ dysfunction or septic shock in Queensland between October 2018 and December 2019, will be included. Children who are deceased at follow-up, under care of the state, or require English interpreters will be excluded from participation. Data will be collected through an online follow-up survey comprising validated caregiver-reported questionnaires covering the four Post Intensive Care Syndrome-paediatrics (PICS-p) domains (cognitive, physical, emotional and social health; Manning et al. Pediatr Crit Care Med, 2018, 19, 298–300).

The primary outcome is an adaptive behaviour of the participants assessed using the Vinelands-3 tool. Secondary outcomes will include neurodevelopment, quality of life, child distress, overall function, executive function, caregiver's distress and caregiver's stress. Analysis of variance (ANOVA), Kruskal-Wallis and Fisher's exact test/chi-squared tests will be used for statistical analyses. No adjustments will be made for

multiple comparisons but it is acknowledged that comparisons made in this study are exploratory.

Relevance to Clinical Practice: With more children surviving sepsis, there is a need for a more comprehensive assessment of patient and family outcomes to allow support structures for families leaving the hospital after sepsis. This study is expected to inform clinicians and stakeholders of patient and family well-being after sepsis survivorship.

KEYWORDS
long-term, outcomes, PICS-p, sepsis, survivorship

1 | BACKGROUND

Surviving sepsis in paediatric populations has shown a growing burden related to long-term morbidities, such as loss of limbs, neurocognitive impairment, post-traumatic stress disorder (PTSD), family dysfunction and implied long-term carer roles.[1–3] Although an estimated 2.5 million children survive sepsis globally each year,[4] evidence is emerging to suggest higher morbidity, with 28%–34% reporting some form of disability at hospital discharge.[1,3,5] In Australian children, sepsis has been reported as the most common disease leading to potentially preventable death.[6] Although sepsis has been flagged as a major health priority, there is limited evidence of long-term outcomes in this population past hospital discharge. The majority of follow-up has looked at short-term recovery time frames between 28 days and 3 months[7–10]; however, there is evidence to suggest that disabilities are still present as far as 12 months after hospital discharge.[11–14] The limited understanding of this population is gaining increased attention in an effort to address statistics, knowledge gaps, and to better understand the impacts of sepsis survival.

More broadly, paediatric intensive care survivorship has demonstrated impacts in a much wider range of domains including functional status, neurodevelopment, quality of life, adaptive behaviour, distress and family dynamics.[15–19] This group has been widely documented in adults as Post Intensive Care Syndrome (PICS).[20] More recently, this concept has been adapted for the paediatric population known as Post Intensive Care Syndrome-paediatrics (PICS-p).[20] Acknowledging the key areas of PICS, the PICS-p framework identifies four key domains (cognitive, physical, emotional and social health) thought to be major impacts to a child's recovery amongst others after critical illness. This concept has attracted attention in the intensive care environment with adaptations emerging in the literature addressing core outcome measures important to recovery (Figure 1).[21–23] Since the conceptualisation of PICS-p, emphasis has been placed on the fact that any one of these outcomes does not occur in isolation but that there is interaction among each other, resulting in a potential lifetime impact on both the child and family.[20]

To date, long-term research on paediatric sepsis survivorship has been scarce with current evidence only exploring sepsis outcomes in PICU environments. In a review exploring long-term outcomes in paediatric sepsis populations in the last 10 years, results showed deficits in areas such as neurocognition, psychological trauma, behavioural changes, and family challenges.[24] Discrepancies in follow-up time frames and variation in assessment tools have limited the overall understanding of the full impact sepsis is having on survivorship morbidity globally.[4,25] The Life After Paediatric Sepsis Evaluation (LAPSE) study was identified as a landmark study on paediatric sepsis outcomes and the only large study that used the influence of the PICS-p concept to understand morbidities in sepsis survivorship.[11] Physical, cognitive and emotional health domains were investigated, with 35% of children surviving at the 12-month follow-up time point reported to have not regained their baseline health-related quality of life.[11] Acknowledging the present evidence to suggest morbidity at 12 months after hospital discharge in this population, it has highlighted the need for further investigations to incorporate more comprehensive follow-up to address this knowledge gap and unknown areas such as social health.

There has been little focus on the outcomes of the sickest children requiring a PICU admission for sepsis, yet not all children receiving treatment for sepsis require an ICU admission. To date, follow-up studies have only focussed on PICU cohorts.[7,8,10,11,26] Considerable recent quality improvement (QI) work has however had a key focus around early identification and treatment focussed on cohorts outside of the PICU.[6,27,28] Appreciating that there is no understanding of the outcomes in these cohorts, there is a need to address these issues to

What is known about the topic

- Thirty percent of paediatric sepsis survivors report some form of impairment at hospital discharge.
- Cognitive, physical, and emotional outcomes have been reported but social health has yet to be understood.

What this paper adds

- New information regarding sepsis survivorship and morbidities two years after hospital discharge.
- The use of the PICS-p framework could aid in better understanding sepsis cohesively across four key domains of health.

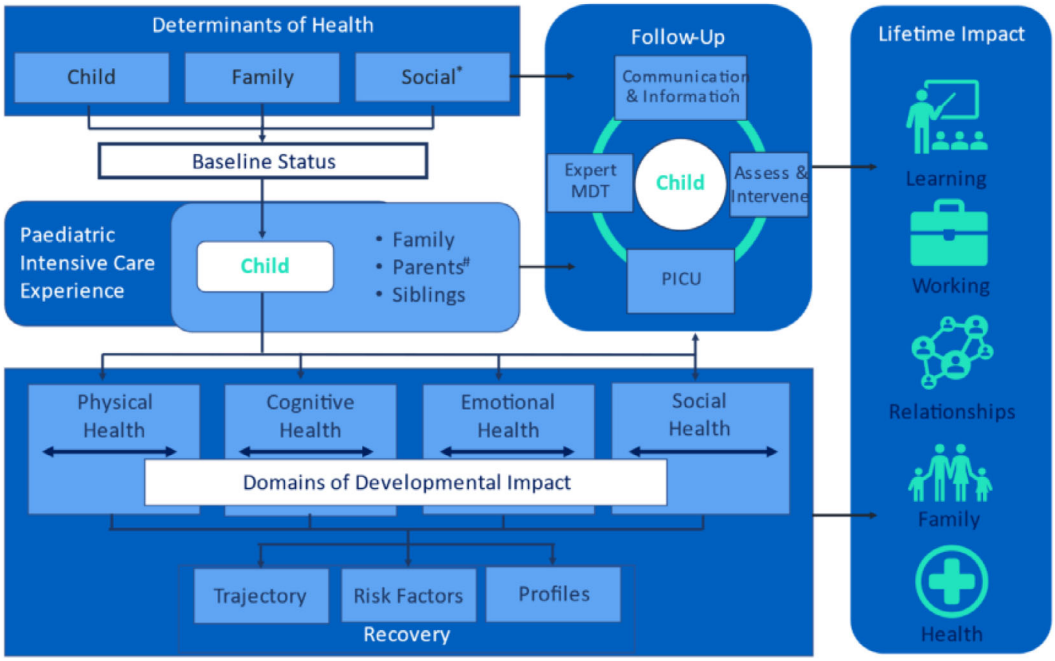

FIGURE 1 Adapted post intensive care syndrome-paediatrics.[21]

completely understand the long-term burden sepsis is having on the paediatric population and develop an understanding of all cohorts of children receiving treatment. The influence of the domains incorporated in the PICS-p concept as previously mentioned provide a uniform way to collectively understand these outcomes. Understanding that sepsis has been reported to significantly impact the PICU population, the purpose of this study is to provide a comprehensive understanding of the long-term outcomes associated with paediatric sepsis survivorship in children treated in a non-PICU environment.

2 | AIMS

The aim of this study is to investigate the long-term outcomes of children surviving sepsis.

2.1 | Design

The Long-term outcomes after paediatric sepsis (LOTUS) study is a state-wide, prospective, observational follow-up cohort study. This study will be reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.[29]

3 | SETTING AND SAMPLE

The *Paediatric Sepsis Breakthrough Collaborative. Improving Outcomes for Children with Sepsis in Queensland-an observational study to measure quality improvement within the collaborative* (Children's Health Queensland Human Research Ethics Committee reference number: HREC/21/QCHQ/80647 is the parent study of the LOTUS study). Selected paediatric emergency departments from 11 Hospital and Health Services (HHSs) across Queensland piloted a sepsis pathway between October 2018 and December 2019 in an effort to identify and treat sepsis earlier in children. All children treated on the pathway ($N = 523$) served as the potential participant group for the LOTUS study. Details on the quality improvement works have been previously published.[6,30]

4 | PARTICIPANTS

Participants will be included if they were cared for on the sepsis pathway (parent study, $n = 523$) and on Senior Medical Officer review deemed to meet the care path criteria for either sepsis associated organ dysfunction or septic shock as defined by the parent study. Criteria for sepsis categorisation can be found in Data S1. Participants will be excluded if they are >18 years of age or deceased at time of follow-up, involved in/under the care of child safety, or where parent/caregiver English literacy requires interpretation services.

5 | STUDY PROCESSES

5.1 | Screening

The participants from the parent study were screened for eligibility using the inclusion and exclusion criteria. Two hundred and thirty-two

children were identified as being treated for sepsis-related organ dysfunction or septic shock. After further screening for any exclusions, 186 children were deemed eligible for participation.

5.2 | Participant contact and consent

Caregivers of eligible children will be notified of the study and invited to participate. The first notification will occur via the Queensland Health Integrated Messaging system by means of an automated text message about the study and access to the participant information sheet. After initial contact, a member of the research team will then phone the caregiver to provide further information, answer any questions and gain verbal consent to receive the electronic questionnaire to complete. A script of intended conversation from first contact to consent can be found in the Data S1.

Up to three attempts will be made to make phone contact with caregivers of eligible participants to gain consent, after which the family will be deemed unable to contact (lost to follow-up). In consenting participants, means to complete the survey via telephone or mail will be offered if an online mode is not accessible. The caregiver will be followed up 7 days after first contact to ensure the survey was received (email/post); any issues with survey delivery and/or completion will be addressed.[31] The participants will then be prompted a maximum of five times, where necessary, for completion of the survey.[31,32] Following this, if the survey is partially completed, data from partially completed surveys will be included if the participant completed at least the primary outcome measure (Vineland −3). If this is incomplete or there is no commencement of the survey, it will be deemed a loss to follow-up. A log of participant contact will be maintained.

To ensure voluntary participation in the study is upheld, there are three points of contact that the participants will be able to opt out from participation.[33] These three points of contact will be at first contact on the telephone when informed of the study, on provision of an email address and prior to survey commencement.

5.3 | Study measures and outcomes

The primary outcome is adaptive behaviour, as measured by the Vinelands-3 Adaptive Behaviour Score (ABC).[34] A normative mean ABC score of 100 with a standard deviation (SD) of 15 will be used to determine adaptive behaviour in the target population. Scores >1 SD below the normative mean will indicate poor adaptive behaviour. This outcome addresses the evidence gap relating to social health after sepsis, as previous literature has focussed on physical, cognitive and emotional outcomes. Secondary outcomes focus on the other PICS-p domains (cognitive, emotional and psychological health) including neurodevelopment, quality of life, child distress, executive function, parent distress and parenting style. Further details regarding the primary and secondary outcomes are provided in Data S1. Each of the outcome measures has been selected based on their validation as parent-reported outcome measures.

5.4 | Data collection

Study data will be collected and managed using the Research Electronic Data Capture (REDCap) system hosted by Queensland University of Technology.[35,36] Using REDCap, data will be collected via a secure online link emailed to the participants containing the survey. The survey will be accessible on any smart device or computer with the ability to save and recommence the survey to allow for survey completion over several sittings if required. The database is password-protected and only accessible to study investigators. Information and data obtained via the survey will be directly stored in the study REDCap database. Data will be stored in a secure location and retained appropriately.

5.5 | Sample size

A sample size of 155 participants will allow the calculation of a two-sided 95% confidence interval (CI) with a width equal to 0.15, assuming the proportion of patients with an ABC score >1SD below the normative mean score of 100 to be 30%.[2–4] With a cohort of 186, and assuming a loss-to-follow-up rate of 15%, this sample size is achievable.

5.6 | Data analysis

Descriptive characteristics of the cohort will be reported using mean (standard deviation), median (interquartile range) and number (percentage), depending on data type. Distribution of continuous variables will be assessed visually through inspection of histograms. Comparison of these characteristics between the participants who consented, non-consenters and those lost to follow-up will be reported. Lost to follow-up will be defined as participants who consented for participation and received participation reminders but either did not commence the survey or had a partially competed survey. Where caregivers completed up to and including the Vinelands, their data will be included in the overall analysis, and they will not be considered lost to follow-up. Completion rates for all questionnaires will be presented as it is anticipated that there will be varying rates of completion. Missing data will not be imputed. Standard statistical tests to compare three groups (analysis of variance (ANOVA), Kruskal-Wallis and Fisher's exact test/chi-squared tests) will be used; p-values will be reported with statistical significance set at the 0.05 level, with no adjustment for multiple comparisons, but with an acknowledgement that comparisons are exploratory.

Outcomes from the questionnaires will be presented using the point estimate and associated 95% CIs and compared to respective normative data. Secondary outcomes will be defined as abnormal if scores ≥1 SD below normative means in one or more subdomains of the Ages and Stages Questionnaire (neurodevelopment <5 years), total score in Strengths and Difficulties Questionnaire (neurodevelopment ≥5 years), total score in Paediatric Quality of Life Inventory

(health-related quality of life), total score in the Paediatric Emotional Distress scale (distress <5 years), total score in the Children's Revised Impact of Events Scale (distress ≥5 years), global executive composite score in the Behaviour Rating Inventory of Executive Function and Behaviour Rating Inventory of Executive Function-preschool (executive function ≥2 years). Caregiver measures will also be compared to normative data with scores ≥1 SD below the mean in the total score of the Kessler-6 (emotional well-being), the total score in the Primary Care–PTSD Scale (distress) and the total stress scale in the Parenting Stress Index–Short Form (parenting stress) representative of abnormal results.

A multivariable model will be constructed to assess potential factors associated with the primary outcome. Because of the explorative nature of the study, a range of risk factors from the treatment, family dynamic and baseline demographics will be examined to identify any possible causal relationships.

5.7 | Ethical and research approval

This study will be conducted in agreement with the NHMRC National Statement on Ethical Conduct in Research Involving Humans. Limited foreseeable risk is anticipated from this study; however, psychological referral and support in the case of abnormal results will be provided by a qualified Psychologist within the research team.

5.8 | Implications

Reduction in childhood mortality related to critical illness has in turn seen an increase in morbidities associated to survival. Recent conceptualisation of the PICS-p framework has emphasized a multifactorial influence that factors such as cognitive, physical, social and emotional health can have on a child's trajectory to recovery.[20] The LOTUS study has therefore been designed to better understand the surviving paediatric sepsis population and their potential long-term morbidities.

5.9 | Limitations

There are some limitations which should be acknowledged within the study. The included cohort were determined based on a clinical pathway which was determined by the Senior Medical Officer (SMO) as a part of a QI project, and the participants were subsequently unaware of this occurring. Because of the design of the parent study, the carepath served as a screening measure in the Emergency Department setting and not a diagnostic tool; therefore, children included in the study were not formally diagnosed with sepsis but instead received proactive early interventions on the basis of high suspicion of sepsis. This could have the potential to introduce selection bias because of to a predetermined cohort used from the parent study. In addition to this, the nature of the follow-up study will not have the ability to capture baseline functioning to compare when analysing the outcomes measured in the survey. Population norms will instead be used for comparative analysis. Furthermore, loss to follow-up and missing data are anticipated because of the longitudinal nature of the study and nil face-to-face presence. The study also acknowledges the bias potentially ensued by the caregiver-reported nature of the follow-up survey.

6 | CONCLUSION

This study will be the first of its kind internationally to investigate long-term outcomes of paediatric sepsis 2 years after a child's hospital encounter, using guidance of the PICS-p framework. It is hoped from this study that a collective understanding of outcomes pertaining to the physical, cognitive, emotional and social outcomes will be obtained, with particular emphasis on adaptive behaviour, an area yet to be understood in the paediatric sepsis population. It is intended that the results will provide a ground level understanding that can be further developed at a national and international level to inform quality improvement initiatives and define needs beyond the hospital stay.

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CONFLICT OF INTEREST STATEMENT

There is not conflict of interest to disclose with this article and the subsequent works.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

This study was conducted in agreement with the NHMRC National Statement on Ethical Conduct in Research Involving Humans. Ethical approval has been granted from Children's Health Queensland HREC/21/QCHQ/80647 and ratified by the Queensland University of Technology Research Ethics Committee.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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