Early Peanut Immunotherapy in Children (EPIC) trial: protocol for a pragmatic randomised controlled trial of peanut oral immunotherapy in children under 5 years of age

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ABSTRACT

Introduction Food allergy is a major public health challenge in Australia. Despite widespread uptake of infant feeding and allergy prevention guidelines the incidence of peanut allergy in infants has not fallen, and prevalence of peanut allergy in school-aged children continues to rise. Therefore, effective and accessible treatments for peanut allergy are required. There is high-quality evidence for efficacy of oral immunotherapy in children aged 4–17 years old; however, few randomised trials have investigated peanut oral immunotherapy (OIT) in young children. Furthermore, the use of food products for OIT with doses prepared and administered by parents without requiring pharmacy compounding has the potential to reduce costs associated with the OIT product.

Methods and Analysis Early Peanut Immunotherapy in Children is an open-label randomised controlled trial of peanut OIT compared with standard care (avoidance) to induce desensitisation in children aged 1–4 years old with peanut allergy. n=50 participants will be randomised 1:1 to intervention (daily peanut OIT for 12 months) or control (peanut avoidance). The primary outcome is the proportion of children in each group with a peanut eliciting dose >600 mg peanut protein as assessed by open peanut challenge after 12 months, analysed by intention to treat. Secondary outcomes include safety as assessed by frequency and severity of treatment-related adverse events, quality of life measured using age-appropriate food allergy-specific questionnaires and immunological changes during OIT.

Ethics The trial is approved by the Child and Adolescent Health Service Human Research Ethics Committee and prospectively registered with the Australia and New Zealand Clinical Trials Registry.

Dissemination Trial outcomes will be published in a peer-review journal and presented and local and national scientific meetings.

Trial registration number ACTRN12621001001886.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Oral immunotherapy (OIT) is recognised as a treatment option for children aged 4–17 years old with peanut allergy that is effective at inducing desensitisation, with some studies also demonstrating improved quality of life. However, there are less data on outcomes of OIT in younger children and no published randomised controlled trials of food-based peanut OIT compared with avoidance in preschoolers.

WHAT THIS STUDY ADDS

⇒ This study aims to evaluate the safety and effect of a pragmatic food-based peanut OIT protocol using parent-prepared doses, including impact on quality of life, during the first 12 months of treatment compared with standard care (peanut avoidance).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study may support the implementation of peanut OIT in clinical practice for young children using a translatable, non-pharmaceutical intervention by providing the evidence for improved patient-important outcomes of OIT compared with existing standard of care of peanut avoidance.

INTRODUCTION

Food allergy is a major public health problem affecting one in ten Australian infants. Peanut allergy is the most prevalent food allergy in children, affecting 2%–3% of <5 years old and usually persists to later in life. Children with peanut allergy are at risk of potentially life-threatening anaphylaxis and have reduced quality of life (QoL) that worsens on reaching school age due to dietary, social and emotional impact.

Despite uptake of infant feeding and allergy prevention guidelines in Australia, the incidence of peanut allergy is unchanged and the prevalence of allergies in children is rising, hence effective treatments for peanut allergy are needed.

Oral immunotherapy (OIT) is an emerging treatment for food allergy, involving daily ingestion of increasing amounts of food...
allergen. There are two possible outcomes achieved with OIT; desensitisation, which is a temporary suppression of allergic reaction while on OIT, and sustained unresponsiveness, involving remission of allergy with long-term protection against allergic reactions after stopping treatment. Most children receiving OIT for peanut allergy are desensitised12-16 but fewer achieve remission.17 18 While remission is associated with a greater long-term reduction in allergic reactions than desensitisation,18 achieving a partially desensitised state (ie, establishing a relatively high eliciting dose (ED) of peanut consumption at which an allergic reaction occurs) has been modelled to significantly reduce the likelihood of peanut allergic reactions from accidental consumption.19 This may lead to reduced food-related anxiety and improved patient empowerment; however, these benefits could be offset by the burden of treatment hence further evaluation of OIT in clinical trials is required.20

International expert guidelines recommended consideration of OIT for children with severe allergy from 4 years of age,21 but not in younger children. Furthermore, OIT is not recommended by 2023 Australian expert guidelines due to uncertainty around efficacy, safety and other patient-important outcomes that should be addressed in clinical trials.20

A peanut OIT (pOIT) product, Palforzia, has demonstrated efficacy in children from 4 to 17 years old after 12 months of treatment14 and has subsequently been approved by some medicines regulators. Theoretical concerns have been raised about potential variability of food products being used in OIT protocols, however, consensus guidelines21 22 supported by published data15 16 recommend OIT can be offered using food products while following standardised, evidence-based protocols.

Administering OIT using readily available food products with doses prepared and administered by parents, rather than compounded by pharmacy or dispensed by health professionals, may improve access to OIT by reducing costs of treatment. However, it is necessary to further investigate the efficacy, safety and tolerability of a pragmatic, food-based pOIT treatment protocol prior to implementation in routine clinical practice.

This paper reports the research protocol for the Early Peanut Immunotherapy in Children (EPIC) open-label randomised controlled trial evaluating the efficacy of pOIT, using caregiver-measured and administered doses of a supermarket food product, at inducing desensitisation in children from 1 to 4 years of age when compared with standard care of strict peanut avoidance.

AIMS
Primary objective
To compare the proportion of participants with a peanut ED>600mg peanut protein in pOIT and control groups, as assessed by open peanut oral food challenge (OFC) at 12 months (end of treatment, EOT).

Secondary and exploratory objectives
To describe the safety of pOIT as assessed by parent-reported treatment-related adverse events and efficacy as assessed by range of EDs at EOT OFC; compare changes in QoL and perception of OIT between groups and during course of pOIT; and describe treatment costs and immunological changes associated with pOIT.

METHODS
Trial design
EPIC is a two-armed, open-label, randomised controlled superiority trial of pOIT compared with peanut avoidance (1:1 allocation).

pOIT=pOIT taken daily for 12 months.
Control=peanut avoidance (standard care, no placebo).

Study setting
This is a single-centre study conducted in a tertiary paediatric hospital (Perth Children’s Hospital, Australia). Food challenges and initiation of OIT will be conducted on a day admission ward, and updosing visits will be conducted in outpatient clinic under the supervision of experienced nursing staff with medical support as required. Between study visits, pOIT will be administered daily by parents at home.

Participants
Fifty children from 1 to 4 years of age with confirmed or highly probable IgE-mediated peanut allergy will be enrolled.

Inclusion criteria
1. Age from 1 to 4 years.
2. Confirmed or highly probable peanut allergy, defined as
   a. Confirmed: positive peanut skin prick test (SPT) (mean weal diameter ≥3mm) or specific IgE (>0.35kU/L) and objective allergic reaction to screening peanut open food challenge.
   b. Highly probable:
      i. Unequivocal past clinical history of allergic reaction to peanut, and at least 1 of the following at screening: peanut SPT mean weal diameter ≥8mm; peanut sIgE>15kU/L; Ara h 2 sIgE>1kU/L.
      ii. Equivocal or no clinical history of allergic reaction to peanut, with at least 2 of the following at screening: peanut SPT at screening ≥8mm; peanut sIgE>15kU/L; Ara h 2 sIgE>1kU/L.

Exclusion criteria
1. History of severe, life-threatening anaphylaxis to peanut prior to enrolment.
2. Use of beta-blockers.
3. Currently receiving any other allergen (food, venom, aeroallergen) immunotherapy, or have received food immunotherapy in the past 3 months.
4. Significant underlying medical conditions that increase risk of adverse outcomes in the event of an allergic reaction, such as severe cardiovascular or respiratory diseases.

5. Persistent, uncontrolled asthma or wheezing episodes.

**Recruitment and consent**

Potential participants will be referred from public and private allergy clinics or recruited from the community. Informed consent will be obtained in accordance with International Conference on Harmonisation-Good Clinical Practice and National Health and Medical Research Council guidelines and documented using Research Electronic Data Capture (REDCap) software hosted on secure Western Australian Department of Health servers.

**Blinding and randomisation**

Participants will be randomised to pOIT or standard care (peanut avoidance), stratified by confirmed or highly probable peanut allergy (as per inclusion criteria) and age (1–2 or 3–4 years old at enrolment). This pragmatic study is unblinded with no placebo, reflecting current standard of care where the alternative to pOIT is peanut avoidance.

**Intervention**

pOIT consists of incrementally increasing daily doses of defatted peanut flour (50% protein by weight, Peanut Butter & Co Pure Peanut powder, New York, USA). This is a commercially available food grade supermarket product that does not require any specialised manufacturing or handling.

**Intervention (OIT) arm treatment protocol**

**Treatment initiation**

Participants receive up to four increasing doses every 20 min to reach a final dose of 15 mg peanut protein. Doses are mixed with a small amount of a food of the participants’ choice. If a participant has an allergic reaction during TI, the next day they commence pOIT dosing at home with the dose immediately below the one that provoked onset of symptoms (ie, doses 1–3). If all doses are tolerated during TI, participants commence pOIT at home with 15 mg of nut protein (dose 4). Any remaining doses not completed during TI will be incorporated into the updosing phase (table 1).

Participants’ parents are provided with standard measuring spoons (1/64–1/4 teaspoons) to dispense daily treatment doses. A suspension of peanut powder in water is prepared by parents to administer doses <10 mg at home if required. Parents will receive training on use of measuring spoons and preparation of suspension (if required) during TI and updosing visits.

**Updosing**

Following TI participants continue the same dose at home daily for 2 weeks. Updosing to the next dose level occurs under clinical supervision in an outpatient setting, with 2 hours of observation postdose. If the increased dose is tolerated, participants continue that dose at home; if there is an allergic reaction during the updosing visit, participants will restart the previously tolerated dose at home from the following day. Updosing will occur every 2 weeks (minimum 6 visits) until the target maintenance dose of 360 mg peanut protein (3/8 tsp peanut powder) is reached.

**Maintenance**

Participants will continue to take daily doses of 3/8 tsp peanut flour until a total of 12 months of treatment is completed (calculated from date of TI visit). Participants can miss up to two non-consecutive doses per week to accommodate requirements of daily life (daycare, sports, school). Dose modifications may be made through this phase according to prespecified criteria for moderate-severe treatment-related allergic reactions, intercurrent illnesses or extended periods of missed doses.

<table>
<thead>
<tr>
<th>Table 1 Peanut OIT dosing schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment phase</td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Treatment Initiation (single day if tolerated)</td>
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<td></td>
</tr>
<tr>
<td>Updosing</td>
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<tr>
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<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Maintenance</td>
</tr>
</tbody>
</table>

N/A, not available; OIT, oral immunotherapy.
Control (standard care) arm
Continued strict avoidance of peanut for 12 months from the date of randomisation.

Primary outcome
Proportion of participants with a peanut ED≥600 mg peanut protein at EOT in pOIT vs control, as assessed by open peanut OFC (pOFC). The primary outcome will be assessed by conducting a pOFC with peanut at EOT, defined as 12 months after treatment initiation in the pOIT group and 12 months after randomisation in the control group.

Secondary outcomes
Patient-reported outcomes
▶ Proportion of participants reporting, severity of and frequency of, treatment-related adverse events.
▶ Change in child (Food Allergy Quality of Life Questionnaire-Parent Form, FAQLQ-PF) and parent (FAQLQ-P, Parental Burden, FAQL-PB) QoL and Food Allergy Self-Efficacy for Parents, FASE-P from baseline to EOT.

Other secondary outcomes
▶ Proportion of participants discontinuing pOIT treatment.
▶ Change in peanut specific IgE and peanut SPT weal size from baseline to EOT.
▶ Proportion of participants with (a) ED≥300 mg, (b) ED≥600 mg and (c) no allergic reaction to 2500 mg peanut protein dose at EOT.

Exploratory outcomes
Patient reported
▶ Change in QoL and parent self-efficacy during pOIT (baseline vs 12 weeks and 24 weeks; 12 weeks and 24 weeks vs EOT).
▶ Parental perceptions of OIT before, during and after treatment, as assessed by Net Promoter Score (NPS) and Patient Experience Survey (PES).

Other exploratory outcomes
▶ Baseline characteristics associated with successful desensitisation following pOIT.
▶ Changes in peanut SPT and sIgE in responders and non-responders to pOIT.
▶ Changes in other immune parameters (humoral, RNA/protein expression, cellular phenotype) associated with pOIT.
▶ Treatment-associated costs of pOIT.

Study procedures
The schedules of procedures are summarised in table 2 (intervention) and table 3 (control).

Baseline assessment
Demographics, personal and family history of atopic disease including participant history of allergic reactions to peanut and other medical history.
Eczema will be assessed using the SCORing of Atopic Dermatitis scoring index.23

Medications
Beta-blockers, anti-IgE monoclonal antibodies and any other form of allergen immunotherapy will be prohibited.
All participants will be prescribed an epinephrine auto-injector and ASCIA Action Plan for Anaphylaxis.

Biospecimen collection

Blood
Venous blood will be drawn in lithium heparin and serum vacutainer tubes. Peanut and Ara h 2 serum sIgE will be measured by ImmunoCAP (Phadia AB, Uppsala, Sweden). Whole blood will be separated for frozen storage of aliquots peripheral blood mononuclear cells (stored in liquid nitrogen), plasma and serum (stored at −80°C).

Stool
Samples will be collected at baseline and EOT using OMNigene GUT kit.

Saliva
Saliva samples will be collected using a cotton swab, centrifuged and frozen.

Skin prick test
Peanut extract (ALK USA) plus negative saline and positive histamine control SPT will be conducted on the forearm of each participant, using Quintips. The average of the longest weal diameter (D1) and the longest perpendicular measurement to D1 will be recorded as the mean weal diameter.

QoL and Parental Perception Questionnaires
The FAQLQ and FAQL-PB are disease-specific health-related QoL for children with food allergy24 and their parents.25 The FASE-P is a validated questionnaire to assess parental confidence in managing food allergy.26 QoL will be measured using FAQLQ-PF, FAQL-PB and FASE-P completed by the same parent throughout.

Parental perceptions of OIT will be measured using NPS, a widely used customer experience metric that has been used to assess patient satisfaction with health services.28

The Patient-Reported Outcomes Measurement Information System Emotional Distress Anxiety Short Form 8a29 30 and the Parent Proxy Short Form 8a31 questionnaires are validated person-centred measures for anxiety in individuals and their children. Parents will complete this questionnaire once at EOS.

The PES is derived from the Australian Hospital Patient Experience Question Set32 developed by the Australian Commission on Safety and Quality in Health Care, modified to suit the trial setting and with additional questions included based on feedback from consumer consultation prior to the trial.

Daily diary
Parents will complete a web-based daily electronic diary directly into REDCap. Diary data will be used to assess
adherence, AEs, accidental peanut ingestion and hospital admissions. Control group will complete a daily diary during month 3 and month 9 to collect background rates of parent-reported AEs.

**Oral food challenge**

An open pOFC will be performed at study entry for those participants who do not meet the criteria for ‘highly probable peanut allergy’, and in all participants at EOT. The OFC will be conducted using an adaptation of the ASCIA peanut challenge protocol, modified to include an additional 600 mg dose step resulting in increments of 10 mg, 30 mg, 100 mg, 300 mg, 600 mg, 1000 mg and 2500 mg peanut protein given at 20 min intervals.

Positive challenges will be defined by an allergic reaction meeting PRACTALL consensus stopping criteria, with severity assessed in accordance with published multidisciplinary expert consensus guidelines. The ED is defined as the amount of peanut protein in the OFC dose given immediately prior to onset of signs meeting stopping criteria.

### Statistical analysis plan

#### Sample size

A sample size of 50 randomised participants allocated 1:1 to pOIT (n=25) or control (n=25) will have a power of 0.85 to detect a difference in proportion achieving the primary outcome of 66% in pOIT and 25% in control with an alpha of 0.05. Recruitment and randomisation of the target participant sample size has been completed. The study is ongoing, with completion of data collection anticipated to be completed in January 2024.

Baseline assumptions of pOIT efficacy were derived from published registry data of preschool pOIT outcomes and a phase III RCT of pOIT in 4–17 years old. The estimated 25% response rate in controls includes participants with naturally high (>600 mg peanut protein) reaction threshold, spontaneous resolution of allergy or rarely misclassification at baseline of a non-allergic participant as having ‘highly probable’ peanut allergy, noting that those with relatively low sIgE and SPT would not be eligible for enrolment in this study based without undergoing an OFC at entry to confirm peanut allergy.

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**Table 2** Summary of schedule of procedures for intervention group

<table>
<thead>
<tr>
<th>Peanut OIT; intervention group</th>
<th>Screening</th>
<th>Treatment</th>
<th>End of treatment</th>
<th>End of study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study phase</strong></td>
<td>Up to −24</td>
<td>0</td>
<td>16–48</td>
<td>52 (up to 56) +4 from EOT</td>
</tr>
<tr>
<td><strong>Visit category</strong></td>
<td>Screening visit</td>
<td>Entry OFC</td>
<td>Initiation</td>
<td>Updosing</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>2 hours</td>
<td>5–6 hours</td>
<td>4 hours</td>
<td>2–3 hours</td>
</tr>
<tr>
<td><strong>Procedure</strong></td>
<td>Informed consent</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Eligibility criteria</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Demographics, medical and family history</strong></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anthropometrics, vital signs, physical exam, SCORAD</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Questionnaires</strong></td>
<td>X</td>
<td>X—12 weeks</td>
<td>X—24 weeks</td>
<td></td>
</tr>
<tr>
<td><strong>Skin prick test</strong></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Blood, stool and saliva samples</strong></td>
<td>X</td>
<td>(X)</td>
<td>X—12 weeks</td>
<td></td>
</tr>
<tr>
<td><strong>Oral food challenge</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse event, concomitant medication assessment</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Anaphylaxis education</strong></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OIT doses at site</strong></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OIT dosing education</strong></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EOT, end of treatment; OFC, oral food challenge; OIT, oral immunotherapy; SCORAD, SCORing of Atopic Dermatitis.
Outcome analysis
Continuous variables will be presented as mean and SD or medians and IQRs depending on distribution of data. For count data rates will be reported, while categorical variables will be presented as frequencies and proportions. For exploratory variables, statistical analyses will be hypothesis generating to inform future studies.

Alpha will be set at 0.05, and 95% CIs reported unless otherwise specified. We will perform between group comparisons for each primary and secondary outcome at the end of the study at 12 months. Efficacy will be determined by comparing differences between groups using a $\chi^2$ test or a Fisher’s exact test (if expected cell counts <5), with difference in proportions reported. ORs will be produced via logistic regression, with adjustment for potential confounders. Secondary outcomes with continuous data (peanut SPT weal size and sIgE) will be analysed using Student’s t-tests or Mann-Whitney U test depending on distribution.

Adverse events will be presented in frequency tables. Exposure-adjusted incidence of treatment-related AEs will be calculated by dividing total trAEs by total pOIT doses taken over a specified period.

Analysis will primarily be on all consented participants in an intention-to-treat analysis. Per-protocol analysis will include only children who complete the study as per the protocol. Deidentified data will be used for outcome analysis.

No interim analysis is planned.

Study oversight, registration, funding, consumer involvement and dissemination
A consumer reference group comprising parents of preschool-aged children with peanut allergy were consulted when developing the study protocol.

The Child and Adolescent Health Service will be the study Sponsor.

The trial was prospectively registered with the Australia New Zealand Clinical Trials Registry (ACTRN12621001001886).

An independent data and safety monitoring committee will be composed of a biostatistician, and two clinical immunologists who have no conflicts of interest with this study.

This work is supported by the Government of Western Australia Department of Health and Channel 7 Telethon Trust through the WA Child Research Fund. The funders have no role in the study design, conduct or analysis.

Results will be published in a peer-reviewed journal and presented at national scientific meetings using grouped and deidentified data only. A consumer reference group, comprising parents of preschool-aged children with peanut allergy, were consulted when developing the

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Table 3  Summary of schedule of procedures for control group

<table>
<thead>
<tr>
<th>Peanut OIT; intervention group</th>
<th>Screening</th>
<th>Standard care</th>
<th>End of treatment</th>
<th>End of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study phase</td>
<td>Screening</td>
<td>Standard care</td>
<td>End of treatment</td>
<td>End of study</td>
</tr>
<tr>
<td>Week of study</td>
<td>Up to −24</td>
<td>0–52</td>
<td>52 (up to 56)</td>
<td>+4 from EOT</td>
</tr>
<tr>
<td>Visit category</td>
<td>Screening visit</td>
<td>Entry OFC</td>
<td>Telephone contact every 3 months</td>
<td>Exit OFC</td>
</tr>
<tr>
<td>Procedure</td>
<td>Informed consent</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Procedure</td>
<td>Eligibility criteria</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Procedure</td>
<td>Anthropometrics, vital signs, physical exam, SCORAD</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Procedure</td>
<td>Questionnaires</td>
<td>X</td>
<td>X—12 weeks and 24 weeks</td>
<td>X</td>
</tr>
<tr>
<td>Procedure</td>
<td>Skin prick test</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Procedure</td>
<td>Blood, stool and saliva samples</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Procedure</td>
<td>Oral food challenge</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Procedure</td>
<td>Adverse event, concomitant medication assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Procedure</td>
<td>Anaphylaxis education</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Procedure</td>
<td>Strict peanut avoidance</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

EOT, end of treatment; OFC, oral food challenge; OIT, oral immunotherapy; SCORAD, SCORing of Atopic Dermatitis.
study protocol and will inform the plan for dissemination of outcomes to participants and the community.

Contributors MDO’S was primarily responsible for the study concept, protocol writing and preparation of manuscript. JM contributed to study design and protocol writing. NB prepared the statistical analysis plan for the protocol. All authors have reviewed and approved the manuscript for submission.

Funding Project funded by the Government of Western Australia Department and Channel 7 Telethon through the WA Child Research Fund.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Child and Adolescent Health Service Human Research Ethics Committee, reference number RGS 4384. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study.

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REFERENCES