Study of Paediatric Appendicitis Scores and Management Strategies (SPASMS): protocol for a prospective multicentre observational study

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Abstract

Background: Abdominal pain is a common reason for children to attend the Emergency Department (ED) with acute appendicitis being the most common surgical cause. Various clinical prediction scores (CPSs) have been developed to assist in determining the risk of appendicitis; however, CPSs have been inadequately validated in children and haphazardly adopted in Australia and New Zealand (ANZ) EDs.

Objective: This study aims to compare and validate various CPSs for diagnosing paediatric appendicitis in children presenting to ANZ EDs.

Methods: This prospective multicentre observational study across ten ANZ EDs is recruiting children 5-17 years presenting to participating EDs with acute right-sided or generalised abdominal pain ?7 days and clinician suspicion of appendicitis. CPSs will

be calculated by the study team from clinician-recorded data and clinician gestalt recorded on a visual analogue scale. Accuracy of CPSs will be assessed by Area Under the Receiver Operative Characteristic Curve and proportions correctly identified as either low-risk or high-risk based on the CPSs published cut-offs. Final diagnosis of appendicitis will be confirmed on histopathology, and the absence of appendicitis confirmed by telephone/email follow-up for those discharged directly from ED.

Results: This study received funding in July 2023 and started enrolment in August 2023. As of October 2024, we enrolled and completed follow up on 1227 participants with an expected end date in mid-2025.

Conclusions: This study aims to determine the best performing CPS for diagnosing pediatric appendicitis in ANZ EDs. Implementation of this CPS in ANZ EDs has the potential to reduce healthcare costs, rationalise the use of healthcare resources, and improve management and outcomes of childhood appendicitis. Clinical Trial: Australian New Zealand Clinical Trials Registry (ACTRN12622001293752): https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12622001293752

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Abstract

Background: Abdominal pain is a common reason for children to attend the Emergency Department (ED) with acute appendicitis being the most common surgical cause. Various clinical prediction scores (CPSs) have been developed to assist in determining the risk of appendicitis; however, CPSs have been inadequately validated in children and haphazardly adopted in Australia and New Zealand (ANZ) EDs.

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Results: This study received funding in July 2023 and started enrolment in August 2023. As of October 2024, we have enrolled and completed follow up on 1227 participants with an expected end date in mid-2025.

Conclusion: This study aims to determine the best performing CPS for diagnosing pediatric appendicitis in ANZ EDs. Implementation of this CPS in ANZ EDs has the potential to reduce healthcare costs, rationalise the use of healthcare resources, and improve management and outcomes

of childhood appendicitis.

Trial registration: This study was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12622001293752) on 6/10/2022.

Keywords: Paediatric; Emergency Medicine; Clinical Prediction Scores; Appendicitis; Abdominal Pain

1. Introduction

Abdominal pain is a common reason for children to attend the Emergency Department (ED), with acute appendicitis being the most frequent cause requiring surgical intervention [1]. Many clinical prediction scores (CPSs) [2-31] have been developed and ED clinicians are encouraged to utilize CPSs to assist with determining the risk of appendicitis [32]. Most CPSs involve calculating a score based on combinations of clinical features and laboratory findings to classify patients into low, intermediate, or high risk. The most frequently used CPSs in children are the Alvarado score [2], Pediatric Appendicitis Score [3], and the pediatric Appendicitis Risk Calculator [4] with each based on different sets of collected variables. Multiple other CPS have been described in the literature, with varying degrees of application and accuracy in children [5-31].

However, CPSs have been inadequately validated in children and haphazardly adopted in Australia and New Zealand (ANZ) EDs [33], resulting in inconsistent practice, with increasing numbers of children exposed to potentially unnecessary imaging and laboratory investigations. This study aims to externally validate multiple CPSs in children aged 5 to <18 years presenting to ANZ EDs with acute abdominal pain with a clinical suspicion of appendicitis and compare the CPSs' performances against local clinician gestalt.

2. Methods

The study is an endorsed Paediatric Research in Emergency Departments International Collaborative (PREDICT) network [34] study with Perth Children's Hospital (PCH) as the lead site. The study received ethics approval from the Child and Adolescent Health Service Human Research Ethics Committee (RGS5295) for Australian sites and from the Northern A Health and Disability Ethics Committee for the New Zealand site (2024 FULL 19738). It was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12622001293752) on 6/10/2022. Each

participating site obtained site governance approval as per their ethics and governance committees.

The study is a quantitative multicenter observational study that measures the performance accuracy of CPSs in identifying surgically and/or histologically confirmed appendicitis. Eligible CPSs were identified in a rapid review by the study authors prior to study commencement [35].

2.1 Objectives

The primary aim of the study is to externally validate various published CPSs for risk of appendicitis in children aged 5 to <18 years presenting to ANZ EDs with acute abdominal pain and suspicion of appendicitis.

The secondary aims of the study are:

i. To evaluate and compare the performance of various published CPSs:

a) against clinician gestalt in ANZ for the likelihood of appendicitis at the time of ED assessment

b) in identifying, prospectively, the likelihood of complex appendicitis (defined as the presence of perforation, extra-luminal fecalith, diffuse intra-peritoneal pus, or a well-formed abscess) [36]

ii. To describe the epidemiology and management of pediatric appendicitis illustrating:

a) the burden of disease in patients presenting with acute abdominal pain with the suspicion of appendicitis,

b) the incidence and type of surgical procedures undertaken in the management of appendicitis in ANZ (laparoscopic appendicectomy, open appendicectomy, non-surgical management with intravenous (IV) antibiotics and delayed appendicectomy),

c) the imaging procedures undertaken in patients assessed for possible appendicitis, and their

accuracy in the detection of histologically +/- surgically confirmed appendicitis

2.2 Study setting and population

The study population will be all children presenting to participating ANZ EDs with abdominal pain. Study sites all have EDs that manage pediatric patients and have a pediatric on-site general surgical service with capacity to provide input, admission and surgical intervention if needed.

1. Perth Children's Hospital (Western Australia, Australia)
2. Children's Hospital Westmead (New South Wales, Australia)
3. Gold Coast University Hospital (Queensland, Australia)
4. Monash Health (Victoria, Australia)
5. Queensland Children's Hospital (Queensland, Australia)
6. Royal Children's Hospital (Victoria, Australia)
7. Royal Hobart Hospital (Tasmania, Australia)
8. Sunshine Coast University Hospital (Queensland, Australia)
9. Sunshine Hospital (Victoria, Australia)
10. Starship Hospital (Auckland, New Zealand)

2.2.1 Participant inclusion criteria

To be eligible to participate in the study, a participant must meet the following criteria:

1) Age 5 years to <18 years

2) Presentation with generalized or right-sided abdominal pain

3) Duration of pain for ≤7 days (i.e. ≤168 hours)

4) Clinician concern for the possible diagnosis of appendicitis as defined by any one of the following:

   i. Investigations performed (bloods/imaging, including external investigations prior to ED attendance)

   ii. Surgical consultation to assess the patient for possible appendicitis

iii. Senior ED clinician consultation to assess patient for possible appendicitis

iv. Period of observation in ED to re-assess patient for possible appendicitis

For those hospitals with mixed ED and limited pediatric surgical capacity to operate on children under a certain age the site-specific “pediatric” age range will be applied (e.g. >10 years and/or < 16 years).

2.2.2 Participant exclusion criteria

The following conditions exclude participation in the study:

1) Abdominal trauma which required medical review within the preceding 7 days

2) Previous significant abdominal surgery (e.g. appendectomy, short gut, ileostomy, Hirschsprung’s disease)

3) Chronic illnesses which may affect the abdomen (including inflammatory bowel disease, chronic pancreatitis, cystic fibrosis, sickle cell anemia)

4) Pregnancy

5) Inability to obtain accurate history (e.g. parent/guardian unavailable, language other than English AND where no interpreter was available, or patients who are non-verbal due to pre-existing medical condition)

2.3 Outcome measures

The primary outcome is the presence of appendicitis; this will be confirmed through the histopathology report when available, or operation report if not available. Patients diagnosed with appendicitis but managed non-operatively will be followed up to confirm the presence of appendicitis in cases where interval appendicectomy was performed or excluded from analysis in cases treated conservatively with antibiotics only. A non-appendicitis diagnosis will be confirmed on follow-up via either: i) recording of the primary diagnosis on hospital discharge if admitted to

hospital, or ii) contact at 30-60 days to ensure no progression in symptoms or representation to hospital for those discharged directly from ED. The area under Receiver Operating Characteristic (ROC) curve will be calculated for the various published CPS for the primary outcome of appendicitis.

Secondary outcomes include rates of uncomplicated and complicated appendicitis (defined as the presence of perforation, extra-luminal fecalith, diffuse intra-peritoneal pus, or a well-formed abscess) [36], negative appendicectomy cases (based on histopathological findings), and missed appendicitis cases. These will be confirmed through the histopathology report when available, and operation report if not available. To identify missed appendicitis cases, families of children who did not undergo appendicectomy and were discharged directly from ED will be contacted within 30 to 60 days of hospital discharge to assess for post-discharge status and whether their child had an appendectomy in the interim. For families unable to be contacted, medical records will be reviewed at 60 days to assess for re-presentation. Other secondary outcome measures include length of hospitalization, rates of investigations and rates of interventions.

2.4 Patient recruitment and data collection

All suitable patients with abdominal pain will be identified on ED presentation and approached by a research nurse (if available) or the treating clinician for consent for a) study participation and data access/collection and b) follow up contact. Patients who are not captured on the index visit (i.e. “missed” recruitment) will be identified by the research team through a review of the daily ED attendance record using the terms “abdominal pain”, “appendix” or “appendicitis” on triage text or discharge diagnosis text “appendicitis” or “abdominal pain”.

Basic demographic data of missed patients (including any interventions performed and management) will be recorded on a separate datasheet and collected at the earliest possible time. Missed cases, if assessed by the research team to be eligible, will have a retrospective case report form completed by the treating clinician, if possible, and the family will be contacted via phone or text message to obtain informed verbal consent for inclusion retrospectively for a) study participation and data access/collection and b) follow up contact. Follow-up will not be conducted for patients who are admitted to hospital under an inpatient medical or surgical team or those who experience severe morbidity such as new diagnosis of chronic illness or permanent disability or are deceased. Participants who decline consent for data access/collection will be excluded from the study. The study recruitment process and timeline are shown in Figure 1.

The treating clinician will complete at the time of the ED visit, or retrospectively if missed initially, a case report form recording:

- demographic data (sex, age),
- eligibility (inclusion and exclusion criteria),
- caregiver verbal consent,
- the clinician seniority and their perceived likelihood of appendicitis on a Visual Analog Scale from 0 being ‘Extremely unlikely’ to 10 being ‘Extremely likely’ and whether this perceived likelihood was formed before or after investigations (bloods and/or imaging),
- history of the presenting complaint (location of initial pain, duration of pain, highest pain score, highest reported temperature during this illness, right lower quadrant (RLQ)/right iliac fossa (RIF) pain on arrival to ED, pain migration to RLQ/RIF, progression of pain, gradual onset of pain, pain pattern, history of pain with walking, anorexia, nausea, vomiting, difficulty with micturition, pothole tenderness, family history of appendicitis, respiratory

tract infection in last 2 weeks, bowel habit), and

- examination findings (RLQ tenderness, RIF tenderness, tenderness worst in RLQ, tenderness outside RLQ, presence of hop/cough/percussion tenderness, degree of rebound tenderness, abdominal guarding, Rovsing's sign, nature of bowel sounds, palpable abdominal mass, abdominal rigidity).

Clinician management will proceed independent of study participation.

All data collected at sites will be transcribed to a Research electronic data capture database (REDCap) [37]. The following additional data will be collected from the patient medical records: blood test results (white cell count, absolute neutrophil count, neutrophilia, C-reactive protein), urinalysis (presence of leukocytes and/or nitrites), which will then allow the various CPSs to be automatically calculated in REDCap.

Between 30 to 60 days after the ED visit, the site research team will collect the following parameters in all eligible patients through a medical record review:

- detailed demographics (postcode, medicare status, race/nationality, referral source),
- pre-hospital management,
- management and imaging undertaken both pre-ED in the community and in the study hospital,
- time-related data (times of triage, clinician evaluation, ED and hospital discharge),
- duration of ED and hospital stay,
- admission status and/or specialty unit consultations including intensive care admission,
- medication use in ED including antibiotics and analgesia,
- related surgical and/or non-surgical interventions,

- other significant pathology or adverse events, including mortality, and
- disposition.

2.5 Follow up

All eligible patients will be contacted for a follow-up survey except when: (a) parent/guardian declined follow-up on initial presentation, (b) participant admitted under an inpatient medical or surgical team with no further re-presentations to ED within the follow-up period of 30 days, or (c) participant identified by site research team to have experienced clinically significant adverse events. Any approved parental contact will occur via a telephone call or email/text with scripts for each contact method provided to participating sites. Follow-up emails will be automatically generated and sent out twice during the follow-up period with identifiable data accessible only to the local study site and the central coordinating study team and will be removed from the REDCap database at 61 days post enrolment date by the local study research team. A maximum of three contact attempts will be made. If more than 60 days have elapsed from the time of presentation, or if there have been three failed contact attempts, the patient follow-up will be regarded as unsuccessful. The medical record for patients unable to be contacted will be reviewed and if sufficient information is documented in the medical record, this information may be used to substitute for the failed contact.

The follow-up survey will determine the following:

- if the child had any problems with abdominal pain since being discharged from ED,
- if the child missed any childcare or school because of abdominal pain,
- if the carers took any time off work because of the child’s ongoing pain, and
- if the child has been seen by another doctor, health professional, or hospital since the visit to the ED.

It will also collect the following details: details of ongoing problems; number of missed days of

school/childcare; number of days off work; types and numbers of medical review; additional medical diagnoses; need for and duration of ED and/or hospital admissions including investigations (with review of the relevant medical record); and related surgical interventions.

Any eligible participants whose parent/guardian consented for data access/collection but declined follow-up will have their data collected and analyzed but will not be contacted for follow-up. If participants withdraw consent and discontinue participation in the study at any time, there will be no effect on their medical care or access to treatment. If a participant is withdrawn prior to completing the study follow-up period, any known reason for withdrawal will be documented in the database. All information already collected as part of the study will be retained for analysis, but no further efforts will be made to follow up or obtain additional information regarding the participant. As an observational study there are no anticipated adverse events related to the research. During the follow-up contacts if any medical issues are identified by research staff, they will be referred to the managing clinicians (for patients in hospital), or site investigator (for questions during follow-up) who will refer, if required, the patient to their general practitioner or ED for review.

To minimize information bias, the calculation of the CPSs will be performed by the research team and not by the treating clinician. If the study participant is transferred from a non-study site to a study site, the data collection form will be completed by the initial treating physician at the study site; if the study participant is transferred from a study site to a second study site, this will ideally be completed by the initial treating physician at the first study site.

2.6 Sample Size and Power Calculation

Based on a feasibility study performed at PCH ED prior to the multicenter study [35], we estimate a true appendicitis rate of 30% in the multicenter study and that all the CPSs will be calculable in at least half of the patient cohort. We aim to have a sample size of 2,400 children with undifferentiated abdominal pain enrolled which will result in all CPSs to be calculable in a minimum of 360 enrolled cases of true appendicitis. This will provide a level of precision such that a 95% confidence interval

around the ROC curve area under the curve (AUC) will range from ± 0.016 for an AUC estimate of 0.95 to ± 0.032 for an AUC point estimate of 0.75 [38]. It will also provide more than 85% power for a two-sided test, with alpha=0.05, to find a difference of 0.05 between two AUCs if both values are ≥ 0.80, assuming the correlation of risk scores amongst appendicitis cases and that amongst non-cases have an average of at least 0.5 [39]. Under this same assumption, if both AUC values are ≥ 0.9, the planned sample numbers would provide more than 90% power to detect a difference of 0.04.

2.7 Statistics and Interim Analysis

We will follow STAndards for the Reporting of Diagnostic accuracy studies (STARD) 2015 guidelines for statistics [40]. The AUC will be calculated for the various published CPSs and the clinician gestalt for the outcome of appendicitis. The sensitivity, specificity, negative predictive value, positive predictive value, negative likelihood ratio, positive likelihood ratio, and missed appendicitis rate will be calculated based on the published cut offs for each score [2-31]. For the pediatric appendicitis risk calculator (pARC), sub-analysis will be performed for the following pARC categories based on previous validation studies [4,41]: ≤5%, 6-15%, 16-25%, 26-50%, 51-75%, 76-90%, and >90% for pediatric EDs and <5%, 5-14%,15-24%, 25-49%, 50-74%, 75-84%, and ≥85% for mixed ED. For clinician gestalt, sub-analysis will be performed for each point on the Visual Analog Scale. The AUC will also be calculated for complex appendicitis to assess the optimal cut-offs for each CPS to detect complex appendicitis.

The best-performing CPS will be identified by the highest AUC. Sensitivity and positive predictive value will be calculated to establish the CPS's ability to identify high-risk patients, and the misclassification rate (proportion of patients identified as low risk who had acute appendicitis) and negative likelihood ratio will be calculated to establish the CPS's ability to identify low-risk patients. Accuracy will be reported as the proportion of patients not misclassified as either low-risk or high-risk as defined by published cut-offs. Baseline analyses of patient characteristics based on the risk

groups as calculated by the best performing CPS will be conducted by presenting simple counts and percentages with interquartile ranges.

3. Results

We have recruited and completed follow up on 1,224 of the planned 2,400 patients as of October 2024, with two sites still to commence recruitment, and it is anticipated that recruitment will be complete by mid-2025.

4. Discussion

Ideally, all patients with abdominal pain would undergo investigations and/or appendicectomy to determine the presence or absence of appendicitis; however, this would increase the rate of unnecessary investigations and potentially the rate of negative appendicectomies should investigations be inconclusive. Therefore, a similar methodology to a previous PREDICT study looking at clinical decision rules for head injuries [42] was adapted using follow up telephone or email contact to establish the presence or absence of appendicitis after discharge from ED. It is possible some patients with appendicitis would be treated conservatively with antibiotics and excluded from the study; however, this would represent a small number of patients as this is an uncommon practice in ANZ. The predictor variables for the 30 CPSs were derived solely from original publications [2-31] and amalgamated into a single case report form developed by the study authors, which may introduce an element of interpretation in terms of the exact clinical terminology used in ANZ ED settings. The difficulty and variability of prospective clinician data collection in busy EDs in completing the case report form may result in a significant proportion of patients with multiple missing variables to calculate all CPSs, and implementation of an appropriate method such as multiple imputation may be required to minimize potential biases that may arise from missing data.

Rates of computerized tomography imaging in ANZ EDs are lower than in the United States [43] due to concerns about radiation exposure and associated lifetime risk of malignancy and the more prevalent use of ultrasound in pediatric abdominal pain in Australian EDs [1]. The validation of CPSs in a different setting to those in which most of the CPSs are derived may be a potential key strength of the study. Finally, our study will assess the accuracy of clinician gestalt in diagnosing pediatric appendicitis and compare it to the best performing CPS, which may provide evidence to support the use of CPS for guiding clinical management in certain settings.

Our study will allow the simultaneous comparative application and validation of 30 CPSs for diagnosing pediatric appendicitis outside their derivation settings. In addition to a high recruitment rate, the study will depend on high follow-up rates to ensure that our results accurately represent the whole population of children presenting to ED with suspected appendicitis. The study findings and subsequent implementation of CPSs in ANZ EDs have the potential to reduce healthcare costs, rationalize the use of healthcare resources, and improve management and outcomes of childhood appendicitis.

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Figure Legends

Figure 1: Study process and timeline

CRF: case report form

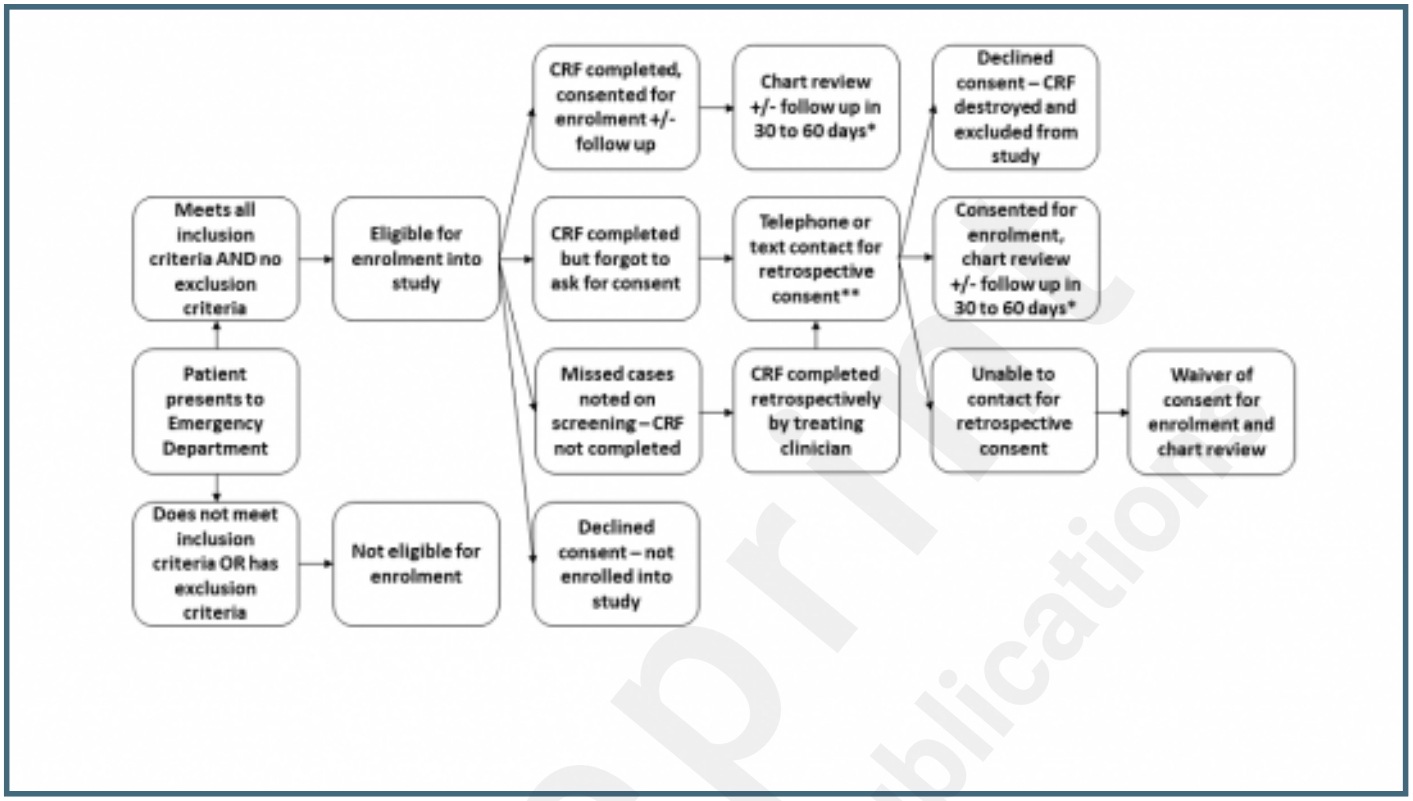
*Dependent on consent and need for follow up

**Contact for retrospective consent can be performed concurrently with follow up in 30-60 days.

Supplementary Files

Figures

Study process and timeline. CRF: case report form. *Dependent on consent and need for follow up. **Contact for retrospective consent can be performed concurrently with follow up in 30-60 days.



Multimedia Appendixes

Project grant application.
URL: http://asset.jmir.pub/assets/841d49816ff5cd334909d04bf20b65c4.pdf

Project grant review and responses.
URL: http://asset.jmir.pub/assets/8f0dc4c4020a631536849da79aee4da2.pdf

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