RURAL: Rural & Urban Risks of Appendicitis CompLications

Comparison of anatomic severity of acute appendicitis in rural and urban paediatric patients: a multicentre, prospective cohort study

Database Website: https://www.ligginstrials.org/

Ethics: Accepted HDEC: **19/NTB/180 - 20/12/2019**

Date and Version No: 21st November 2019 – 1.4

Universal Trial Number: U1111-1236-1865

ANZCTR Trial ID: ACTRN12619001191189p
http://www.ANZCTR.org.au/ACTRN12619001191189p.aspx

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Sponsor:	Northland District Health Board
Funding:	AMRF Doctoral Grant
Data Management & Safety:	Liggins Institute, Central Coordinating Research Hub

There are no potential conflicts of interest to declare.

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1. STUDY COORDINATION & CONTACT PAGE

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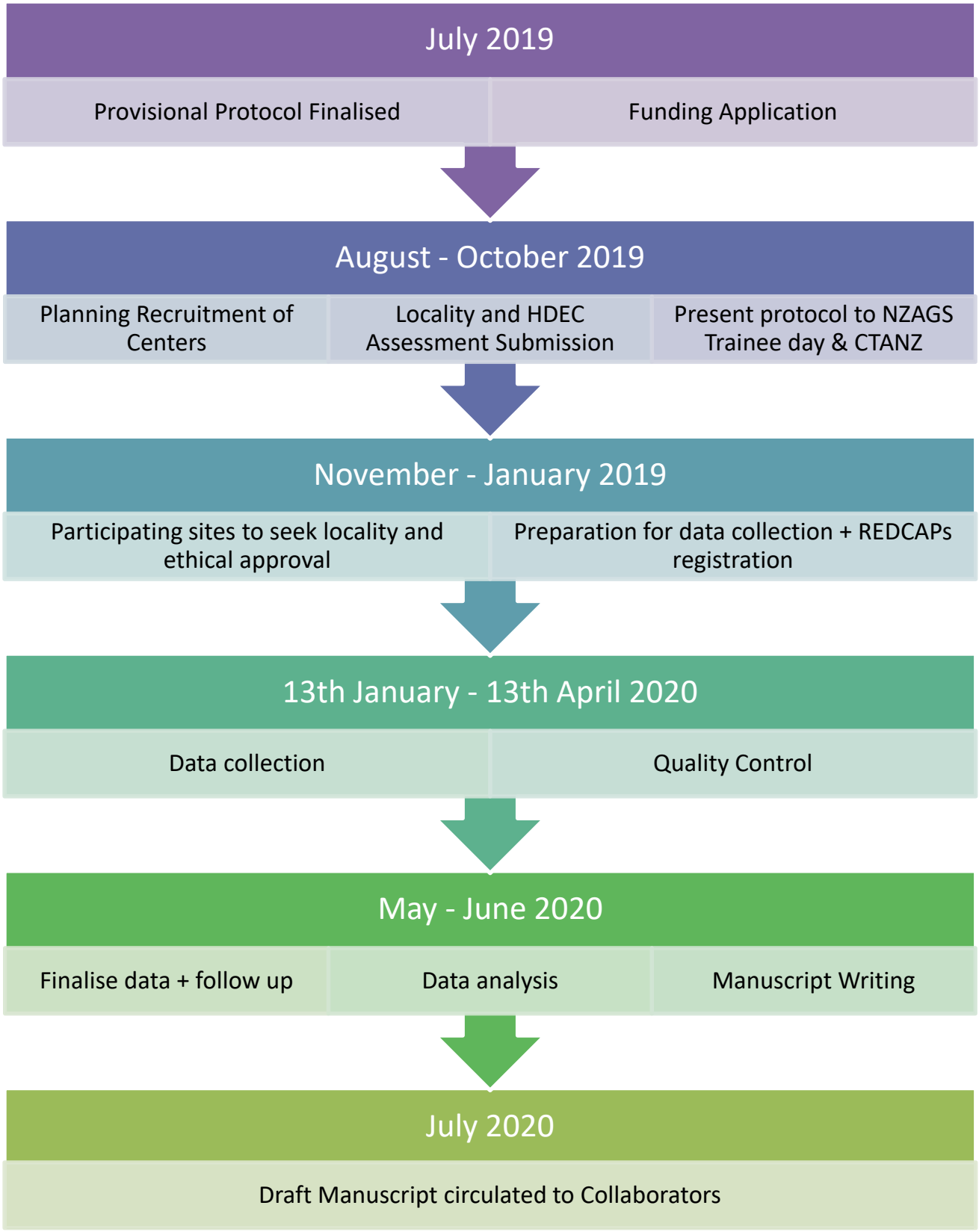
2. STUDY TIMELINE



3. SYNOPSIS

Study Title	Comparison of anatomic severity of acute appendicitis in rural and urban paediatric patients: a multicentre, prospective cohort study	
Internal ref. no. / short title:	RURAL: **R**ural & **U**rban **R**isks of **A**ppendicitis Comp**L**ications	
Study Design	Multicentre prospective observational cohort study.	
Study Population	Paediatric patients (aged ≤16) who present to hospital and are managed for proven or suspected appendicitis.	
Eligible Centres	Any hospital in New Zealand that perform acute appendicectomies on paediatric patients during the study period.	
Planned Sample Size	291	
Outcomes		**Outcome Measures**
Primary	Effect of rural patient status on anatomical appendicitis severity.	American Association for the Surgery on Trauma (AAST) Grading System for Anatomic Severity of Appendicitis.
Secondary	▪ Determine the effect of rurality on clinical severity and post-operative complications ▪ Profile differences in pre-hospital patient behaviour on in-hospital disease severity & perforation. ▪ Provide a national & representative 'snapshot' of appendicitis management.	▪ Paediatric Appendicitis Score (PAS) & Clavien-Dindo Post-Operative Complication Grade. ▪ Travel distance, ethnicity, prehospital delay, mode & access to transport, number of other dependent children. ▪ National incidence, negative appendectomy rate, operative intent
Follow Up	Participant's data will be recorded during their index admission and a 30 day follow up will be performed to assess for post-operative complications.	
Data Collection Period:	13th January 2020 and 13th April 2020.	

4. ABBREVIATIONS/TRANSLATIONS

CI	Co-ordinating Investigator
DHB	District Health Board
CF	Consent Form
HDEC	Health and Disability Ethics Committees
PIS	Participant/ Patient Information Sheet
Whānau	Family – often an extended family when compared to New Zealand European families.
AAST	American Association for the Surgery of Trauma
PAS	Paediatric Appendicitis Score

5. BACKGROUND AND RATIONALE

Appendicectomy is the most commonly performed emergency general surgical procedure on children.[1,2] Rural patient status has been routinely associated with poorer appendicitis outcomes in the United States,[3,4] Canada,[5,6] Taiwan,[7] and South Africa.[8,9] Pre-hospital patient factors such as health-seeking behaviour and reduced access to care are thought to explain a majority of this difference rather than differential management following hospital presentation.[3,5,6,9–14] As a result, appendicitis outcomes in children has been used as a proxy for paediatric access to timely surgical care.

Dependent populations such as children have extremely limited capability to modify geographic and socioeconomic determinants of their health. As a result, they are likely to bear the brunt of any potential disadvantages of rural living such as reduced rates of employment, vehicle ownership, health literacy, and access to telecommunications.[15] Compounding this, the average rural family unit has a higher number of dependent children, placing further strain on families with already limited time and resources.[15]

In 2018, approximately 25% of people in New Zealand lived in a 'small urban' or rural area, defined by Statistics New Zealand as having a population of less than 10,000.[16] In the same year, 53% of New Zealanders lived outside a centre with a dedicated paediatric surgical unit. As such, regional hospitals are expected to deal with non-paediatric specific emergencies in paediatric populations – appendicectomies being the most common example of this. We recently performed a 10-year retrospective study in Northland, New Zealand which revealed that rural children were much more likely to have an increased anatomical severity of appendicitis (OR 2.04), worse Clavien-Dindo postoperative complication grade (p=0.001) and a longer median length of stay (2.5 days vs 2.2 days; p=0.029).[17]

If existing on a national scale, an inequity of this magnitude would be in direct conflict of the Ministry of Health's stated priority of ensuring comprehensive, quality services for people living in rural areas.[18] The Royal Australasian College of Surgeons similarly states that rural patients have a right to a comparable quality of surgical services to urban populations, especially with regards to non-specialist, emergency surgery.[19]

Reduced access to healthcare and delays in obtaining surgical treatment is associated with worse outcome in patients with acute appendicitis.[3,5,9,14] It is hypothesised that rural children at higher risk of poor outcomes in a time-dependent surgical pathology such as appendicitis. However, no study has investigated this in the unique New Zealand environment in a prospective manner and whilst controlling for prehospital patient factors. This project seeks to provide a snapshot of paediatric appendicitis management nationally, investigate differential outcomes and identify any health inequities. This will enable health care providers and funding agencies to improve access and outcomes for this large cohort of New Zealanders.

6. AIMS

We aim to define the effect of rural patient living on the national outcomes of paediatric appendicitis. This is a common and time dependent pathology that can act a benchmark proxy for access to acute paediatric surgery. In order to enable robust comparison between rural and urban children our study will not only account for in-hospital variables but accurately measure prehospital duration of symptomology and investigate prehospital health seeking behaviour and the prevalence of barriers identified by our previous qualitative study.

7. OBJECTIVES

7.1. Primary Objective

Define the effect of rurality on anatomical appendicitis severity in New Zealand children.

7.2. Secondary Objectives

- Define the effect of rurality on clinical severity of appendicitis and 30- day post-operative complications of acute appendectomy.
- Determine the relationship between delay and appendiceal perforation in New Zealand.
- Provide a three month "snap-shot" of paediatric appendicitis outcomes and management.
- Identify prevalence of specific pre-hospital barriers to acute paediatric surgical care.
- Identify predictors of complicated appendicitis in New Zealand children.
- Determine the accuracy of preoperative clinical paediatric appendicitis score

8. STUDY DESIGN

8.1. Type of Study

Multicentre, prospective, observational cohort study led by surgical trainees and junior doctors.

Collaborators at each site will prospectively record routinely collected data on eligible patients over the data-collection period. Following recruitment and consent, data will be prospectively identified from clinical notes, intraoperative findings and histopathology reports. This will be supplemented by a brief parent/caregiver questionnaire to identify potential barriers in accessing timely surgical care

8.2. Patient Identification

Collaborators will identify suitable participants that meet the inclusion criteria through their admission to a paediatric/general surgical ward for suspected appendicitis. This inpatient population realistically encompasses all children with suspected or proven appendicitis. To maximise external validity and ensure particular population groups aren't underrepresented we will utilise an electronic screening database managed by the University of Auckland Liggins Institute Central Coordinating Research Hub. This is separate from the trial database and provides an auditable record of demographic factors such as age, ethnicity, address, NHI and eligibility criteria of participants considered for enrolment. This is only able to be accessed by data managers and the co-ordinating investigator. Once recruited this data will be fully de-identified and a study ID will be assigned for each participant.

Collaborators will be surgical doctors or trainee interns already working on the ward and therefore can liaise with ward staff to identify suitable participants. Children should not be approached without a member of family present. Patients are not required to be identified for recruitment in the Operating Theatre Complex or Emergency Department as these environments are identified to compound unnecessary stress for families.

8.3. Data Collection Period

Data collection is planned to take place between 13th January 2020 and 13th April 2020, however may be feasibly delayed to allow locality assessment processes at each centre. Each centre will collect data on all eligible patients undergoing surgery during this period. Follow-up data will also be collected for up to 30 days after surgery. The final date for 30-day-follow up data collection will be 13th May 2020.

8.4. Study Setting & Methodology

All hospitals in New Zealand that perform acute appendicectomies on paediatric patients will be invited to participate. Following HDEC ethics approval, all participating centres will be required to obtain locality assessment and demonstrate Māori consultation prior to commencement of data collection.

This multicentre, trainee-led collaborative method has been used extremely successfully to enable New Zealand centres to participate in multicentre observational trials in the past (see: the IMAGINE Project HDEC 17/CEN/210). This project would represent the first *locally* established project of this nature.

We have received backing and support from the Clinical Trials Network of Australia and New Zealand (CTANZ) (https://bit.ly/2nlyxyb) which is a network created by the Royal Australasian College of Surgeon's Section of Academic Surgery to supporting trainee-led research in Australasia . Medical students are also expected to become collaborators and we will utilise the Auckland University Surgical Society and Otago Medical School Student Association to reach potential medical student collaborators.

9 OUTCOMES

9.1 Primary Outcome

The primary outcome is the comparison of Anatomic Severity of Appendicitis (as defined by the American Association for the Surgery on Trauma (AAST) Grading System)[20] between rural and urban children.

This system provides a more complete picture than the binary outcome of perforation and has been validated in both high[21] and low income countries[14] as well as children.[22]

The overall AAST grade is defined as the highest grade recorded among the following components: clinical, radiographic, operative, and pathologic. It requires assessment of preoperative factors, macroscopic operative findings and is confirmed by histo-pathologic assessment.

As such collaborators will be expected to record and synthesise the data from those domains. Any disagreements between collaborators should be promptly raised with the supervising consultant and the Co-ordinating investigator for confirmation.

When the disagreement is regarding operative description of the appendix and a consensus cannot be agreed upon then the histopathologic results will provide the basis of the AAST grade due to their objective nature –e.g. an appendix described as mildly inflamed by the operating surgeon which histologically has no evidence of inflammation will be defined as a Grade 0 or negative appendicectomy.

Figure 1: American Association for the Surgery on Trauma (AAST) Grading System for Anatomic Severity of Appendicitis[20]

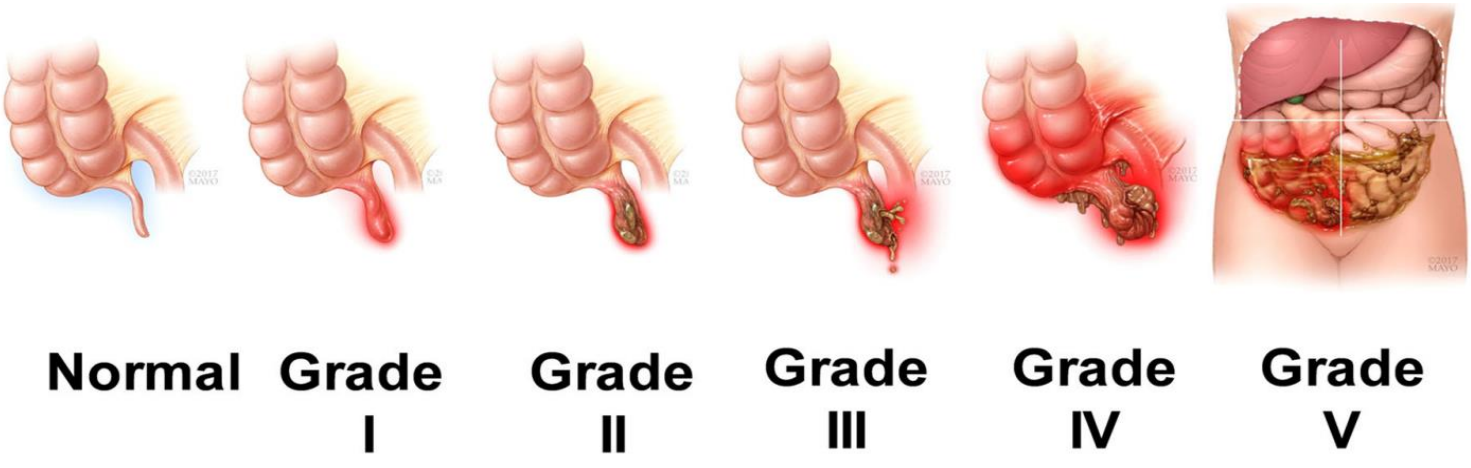


Table 1: AAST Grading System for Anatomic Severity of Appendicitis[20]

AAST GRADE	I	II	III	IV	V
Description	Acutely inflamed appendix, intact	Gangrenous appendix, intact	Perforated appendix with local contamination	Perforated appendix with periappendiceal phlegmon or abscess	Perforated appendix with generalised peritonitis
Clinical Criteria	Pain, leukocytosis and right lower quadrant (RLQ) tenderness	Pain, leucocytosis and RLQ tenderness	Pain, leucocytosis and RLQ tenderness	Pain, leukocytosis and RLQ tenderness; may have palpable mass	Generalized peritonitis
Operative Criteria	**Acutely inflamed appendix, intact** (defined as pathologic erythema, vascular congestion, fibrinopurulent serosal exudate or appendiceal dilation)	**Gangrenous appendix, intact** (defined as appendiceal wall that is friable, purple, green or black)	**Grade II with evidence of local contamination** (defined as fluid confined within a 10-cm radius around the appendix and directly contiguous to the appendix perforation)	**Grade III with regional abscess or phlegmon** (defined as a collection of purulent material greater than 5 cm directly contiguous to the appendix perforation)	**Either grade III/IV with addition of generalised purulent contamination away from appendix**
Pathologic Criteria	Presence of neutrophils at the base of crypts, submucosa +/- in muscular wall	Mucosa and muscular wall digestion; not identifiable on hematoxylin and eosin stain	Gross perforation or focal dissolution of muscular wall	Gross perforation	Gross perforation
Imaging Criteria (CT)	Inflammatory changes localized to appendix +/- appendiceal dilation +/- contrast non-filling	Appendiceal wall necrosis with contrast nonenhancement +/- air in appendiceal wall	Grade II with local periappendiceal fluid +/- contrast extravasation	Regional soft tissue inflammatory changes, phlegmon or abscess	Diffuse abdominal or pelvic inflammatory changes +/- free intraperitoneal fluid or air

9.1.1 Covariates

In addition to demographic, procedure and outcome data, the following data will be collected on confounding Prehospital variables to permit accurate risk adjustment of outcomes (see appendix B). This data will provide valuable information of a participant's prehospital journey.

- Duration of prehospital symptoms in hours (calculated from time & date of symptom onset).
- Travel distance to hospital (km) as calculated from geocoded address in ArcGIS software.
- NZDep 2013 Socioeconomic Deprivation Decile as calculated by geocoded address in ArcGIS software.
- Statistics NZ 2019 Rural/Urban Classification as calculated by geocoded address in ArcGIS software.

9.2 Secondary Outcomes

- Accuracy of preoperative paediatric appendicitis score (PAS).[23]
  → Most well validated clinical score of paediatric appendicitis.[1] (see appendix A)
  → This is measured by **pre**-operative data points collected from ED or ward notes.
- Accuracy of biochemical markers with severity of appendicitis (WCC/CRP/serum Sodium)
- Overall 30-day post-operative complication rate– defined by the Clavien-Dindo Scale[24] (see below)

Table 2: Explanation of Clavien- Dindo Post-Operative Complication Scale.[24]

Grade	Definition (examples listed in italics)
I	Any deviation from the normal postoperative course without the need for pharmacological (other than the "allowed therapeutic regimens"), surgical, endoscopic or radiological intervention. Allowed therapeutic regimens are: selected drugs (antiemetics, antipyretics, analgesics, diuretics and electrolyte replacement), physiotherapy and wound infections opened at the bedside but **not** treated with antibiotics. *Examples: hypokalaemia treated with K; nausea treated with cyclizine; acute kidney injury treated with intravenous fluids; post-op pain treated with anything stronger than paracetamol/ibuprofen*
II	Requiring pharmacological treatment with drugs beyond those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included. *Examples: Surgical site infection treated with antibiotics; deep venous thrombosis treated with enoxaparin; pneumonia or urinary tract infection treated with antibiotics; blood transfusion for anaemia.*
III	Requiring surgical, endoscopic or radiological intervention *Examples: Interventional radiology procedure, return to theatre. Any procedure requiring anaesthetic – eg Ileus requiring PICC line for parenteral feeding,*
IV	Life-threatening complications requiring critical care management, neurological complications including brain haemorrhage and ischemic stroke (excluding TIA). *Examples: Admission to intensive care unit for critical care management. Single or multiple organ dysfunction requiring critical care management, e.g. pneumonia with ventilator support,*
V	Death of a patient

9.3 Parental Questionnaire

As prehospital factors have been routinely reported as the most reliable association with worsening outcome in appendicitis.[8,12,25–30] However only two studies have investigated specific patient-related or systemic factors leading to prehospital delay. Both of these studied adults who underwent appendicectomy; a single-centre study from South Africa[31] which divided prehospital delay "assessment" and "behavioural" and a single-centre study from China[32] that associated prehospital delay with a complex host of psychosocial and demographic information such as coping strategies and personality type.

The domains of our prehospital questionnaire were developed from a qualitative sub-study supplemented by factors from documented in published literature. We interviewed with ten separate rural Northland families who had presented with a child who underwent an appendicectomy, discussing their prehospital journey and any issues faced. This questionnaire covers important prehospital domains such as illness recognition, first-line health seeking behaviour, familiarity with the disease, method of escalation of care, opportunity cost of presentation, physical access to hospital and patient-reported perception of delay.

Collaborators will ask the parents/caregivers of the child several brief questions to obtain the following information about a family's pre-hospital journey (see appendix C):

Pre-Hospital Data Point	Recorded Outcome
Time of symptom onset: (If a symptom other than pain please also record when pain was reported/started)	Time and date.
Was this a school/work day?	Yes/No
Main symptom of child on presentation:	As reported by caregiver/parent. eg, pain, fever, diarrhoea, vomiting, anorexia etc.
Did you a caregiver in your household have to take time off work to bring your child to hospital?	Yes/No
If time was taken off work was there adequate household income to allow this?	Yes/No
Approximate total household income.	Income band
Have you had any friends or family who have had appendicitis?	Yes/No
Presence of health seeking behaviour from friends or family:	Yes/No
Presentation of family to another health service ***prior*** to treating hospital:	Whitecross, Primary Care, Rural Hospital
Who made the decision to present to hospital?	Mum, dad, joint parental, other family member, school, health professional.
Method of transport to hospital for this admission	Private vehicle (own), private vehicle (borrowed), ambulance, etc..
Total number of dependent children	Of caregiver that brought the child to hospital.
Family reported presence of any Prehospital delay	Yes/No + Explanation (Free Text)
Self-Reported Ethnicity of Parent/Caregiver*	Standard MoH ethnicity question

Māori consultation recommendation as generic NHI linked ethnicity underestimates Māori by up to 20%.

10 PARTICIPANTS, RECRUITMENT & CONSENT

10.1 Number of Participants

We will aim to prospectively recruit 291 inpatient cases of paediatric patients who have been admitted to hospital and treated for radiologically- or histologically-proven appendicitis.

10.2 Recruitment

Participants will be prospectively identified by local teams whilst an inpatient in a general or paediatric surgical ward. The caregiver will be approached; the study introduced and informed consent obtained to participate in the study. If the child is aged above 7 years old then an age-specific assent process will be undertaken.

It is **imperative** that participants are approached at a considered time as to not add unnecessary disturbance to families at this potentially distressing time. The study team acknowledges inter-hospital variance of admission and acute theatre processes but in general, unsuitable times include prior to medical stabilisation in the emergency department or whilst the child is in the operating theatre complex.

Collaborators should invite **all** participants that meet the eligibility criteria. To ensure participation is representative, involvement of local Māori cultural support services departments is suggested.

Strategies to identify consecutive patients could include:

- Daily review of emergency department admissions.
- Daily review of handover sheets and ward lists.
- Daily review of acute theatre logs.

10.3 Eligibility Criteria

Participants will be recruited to the study only if they meet all the inclusion criteria and none of the exclusion criteria.

10.3.1 Inclusion Criteria

- Aged 16 or below and admitted to an acute surgical ward for investigation and/or management of suspected appendicitis.
- Underwent or is planned to undergo acute operative or procedural management for suspected/proven acute appendicitis. (INCLUDES 'negative appendicectomies') **OR** child has definitive diagnosis of acute appendicitis on imaging and is being managed conservatively.
- Has a legally acceptable representative capable of understanding the informed consent document and providing consent on the participant's behalf

10.3.2 Exclusion Criteria

- Was transferred to another District Health Board **pre-operatively**
  – however the receiving centre is able to enrol this patient.
- Admitted for an elective appendicectomy for a previous episode of appendicitis.
- Discharged without diagnosis of appendicitis and didn't undergo acute appendicectomy.
- Inability or unwillingness of participant or legally acceptable representative to give written informed consent.

10.4 Participant Involvement in Project

The prehospital barriers investigated by this project have been derived through direct involvement and discussion with local families and consumers of recent hospital care for paediatric appendicitis. The questionnaire was developed from a qualitative study where we visited the houses of rural Northland families. During these visits we discussed the family's experiences in recognising their child's illness, their escalation of care and journey in accessing hospital. Specific barriers, concerns and protective factors were expanded on and explained in the greater context of each family. This allowed previously unconsidered barriers to be identified and for the study team to understand what is important for families rather than the study team telling families what they think the barriers to care are.

11 MĀORI CONSULTATION & TIKANGA

11.1 Impact of Appendicitis on Māori

Appendicitis is an extremely common disease and any intervention that helps improve outcomes in this population will have a great flow-on effect for Māori. Appendicitis is particularly relevant for Māori due to a higher proportion of younger age groups. For example, in Northland, 45% of under-15-year olds identified as Māori. This mirrors the local Northland rates of appendicitis where about 43% of paediatric appendicectomies in the last 10 years were on Māori children.[17]

Compounding this, Māori are unjustly overrepresented in negative socioeconomic statistics that are associated with worse outcomes in appendicitis such as lower median income, rurality and reduced access to primary care. In Northland we found inequities in access and subsequent surgical outcome between Māori and Non-Māori children. Over the last 10 years, we found that Māori children were more likely to live further from the treating hospital (61.7km versus 27.9 km; P = 0.006), live in a lower socioeconomic area, and were more likely to have perforated appendicitis (28.9% versus 19.0%; P = 0.014).[17]

11.2 Benefit of this Study for Māori

The reasons aren't yet clear exactly why inequity in appendicitis outcomes exists but it's suggested to involve a combination of factors that impact families prior to arriving in hospital. However, it is clear that this disparity needs to be further investigated to allow for meaningful and effective intervention. We have incorporated Māori and Rural participant-identified barriers to accessing acute paediatric surgical care and plan to investigate their prevalence on a national scale. The parental questionnaire identifies if there was a delay and why this was the case. This will help us understand how best to help our population and provide valuable evidence to direct public health intervention to better the outcomes of Māori and Non-Māori children across the country.

11.3 Māori Cultural Assessment

Local Māori cultural assessment with the Northland Kaunihera Kaumatua and Te Pou Tokomanawa service has been undertaken. It is expected that each locality will have a separate cultural approval process that undertaken, reflecting heterogeneity of iwi and hapu concerns across the country. Proof of this approval is required at each centre before the study starts.

11.4 Māori involvement in Research Design

Our initial 'proof of concept 'retrospective observational study had identified that 43% of Northland children who underwent appendicectomy identified as Māori.[17] Accurate representation of Māori was extremely important moving forward in our subsequent qualitative study investigating a family's prehospital journey in accessing surgical care for paediatric appendicitis. We approached families at a considered time, extended an open invitation to the greater whānau, held the hui at a familiar place of their choosing and familiarity (usually driving rurally to the whānau's home) and respecting a family's time by offering koha. As a testament of our warm and welcoming community, 50% of the interviewed families identified as Māori and their experiences and perspective shaped our approach to this project.

11.5 Identification of Potential Cultural Issues

It is vital to the integrity of our study that Māori children are fairly represented and that all children with appendicitis have the opportunity to participate. The study team is aware of the vital importance of both

mana tangata and whānau in Te Ao Māori. In order to respect this, we will emphasise collective engagement in the informed consent process. A considered and non-assuming approach will be used when recruiting participants in hospital. Nurses and ward staff will be consulted to ensure that the family isn't approached at an inappropriate time, such as during deliberation, emotional distress or sleep. Brief information and the PIS will be provided to the families followed by independent time for the parents/caregivers to consider whether they would like to consult their friends or whānau regarding this study. If this is opted for, then a suitable time and place will be arranged to allow for dialogue between study collaborators and whānau. Informed consent will only be obtained if this process is followed and participants and their whānau are respected.

12 FOLLOW-UP

Patients will be followed for 30 days after surgery. All secondary outcome measures will be recorded if they occurred at any point from post-operative day 0 (day of surgery) to Day 30.

No change to normal follow-up should take place. Collaborators should be proactive in identifying follow-up data, but this should be done according to the limits of normal follow up at their hospital.

Strategies for follow-up include:

- Regularly reviewing patient notes to identify in-hospital complications
- Participating in daily ward rounds and doctor reviews
- Reviewing clinic notes and clinic letters, if seen in clinic by 30 days
- Checking electronic systems and handover lists for re-admissions
- Checking for emergency department re-attendances

13 CONSENT / ASSENT

The child's parent, caregiver or legally acceptable representative must personally sign and date the latest approved version of the Informed Consent form before any study specific activities are undertaken.

Written and verbal versions of the Parental/Caregiver Information and Informed Consent will be presented detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

For all children above age seven, the child will have the study and their involvement discussed in an assent process including an age appropriate verbal discussion and PIS/CF. The family will be allowed as much time as wished to consider the information, and the opportunity to question the collaborator, their GP or other independent parties to decide whether they will participate in the study.

Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Co-ordinating Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site and uploaded to the electronic study database. If a locality has access to tablets for participant usage then our server will allow an electronic consent process using the exact same forms and an electronic copy will be sent to the participants email.

14 EXAMPLE DATA COLLECTION FLOWCHART

Patient Screening

- Collaborators to work with local admissions units and surgical wards to identify paediatric patients who have been admitted to hospital with suspected appendicitis.
- All such patients are entered into a screening database to ensure particular population groups aren't excluded
- Patients can be recruited post-operatively providing they are still in hospital.

Patient Recruitment

- Approach family at a time of minimal stress and ideally during 'office-hours ' and introduce the study.
- Provide PIS and obtain age-specific assent and parental consent.
- Provide a copy of the PIS and consent/assent forms for participants and one for study records.

Preoperative Data Collection

- Check admission note/daily ward round notes to collect these data points.
- Record the documented pre-operative blood test results & observations in ED/admissions unit/ward.
- Preoperative clinical data collection is from clinical records - **no** additional observations/interventions required of child.
- Provide brief questionnaire to caregiver/parent regarding prehospital journey BEFORE patient discharge

Intraoperative Data Collection

- Time, date, operative approach.
- AAST Anatomical Severity Grade and intraoperative findings.
- If not able to be there please ask operating surgeon first thing in morning and consult operation note..

Postoperative Data Collection

- Discharge Time & Date and hospital Length of Stay.
- Any post-operative complications recorded before discharge and their Clavien Dindo Grade.

Final Follow up

- Check and record histopathology results
- 30-Day post operative follow up. Check clinical note system for readmission, ED presentations or antibiotic prescriptions.
- Ensure data sheet and REDCap record is correct and finalised.

15 QUALITY ASSURANCE

15.1 Team Structure

Each collaborative team should include two-three individuals, one of which is required to be a surgical Registrar or Trainee. It is a requirement that the also be registered with a supervising consultant (attending) surgeon at each site.

15.2 Site-Specific Leadership

Each centre will have a surgical registrar or surgical trainee who will act as a **local lead.** These individuals are responsible for the establishment and day-to-day organisation of the study at their centre. Their role includes the following:

- → Act as a link between mini-teams and study coordinators.
- → First point of contact for local collaborators.
- → Ensure local study outcomes are reported back to clinical teams.

15.3 Consultant Surgeon Supervision

The consultant sponsors registration of the study and ensures collaborators act in accordance with governance guidelines. They should assist with ethical/local approvals and facilitate presentation of local results.

15.4 Co-ordinating Investigator Support

The Co-ordinating Investigator will meet each local lead physically or via video conferencing **prior** to study establishment to provide training and tips into running the project at their site. In addition to this, several clarification documents and an explanatory data sheet will be provided to each centre. Regular meetings/progress reports with local leads will be scheduled to troubleshoot and ensure data quality. Each local lead will have direct access to contact the CI via phone or email to discuss issues.

15.5 Expectations of Collaborators

Collaborators will be expected to behave in a culturally appropriate manner and follow ethical practices otherwise will face exclusion from the study team. Any issues or concerns should be directed to the co-ordinating investigator as soon as practical**.**

15.6 Data Completeness

Following data collection, only data sets with >95% data completeness can be accepted for pooled national analysis. Unfortunately, sites with >5% missing data points cannot be included in the study and collaborators from those sites must be withdrawn from the publication list.

16 STATISTICAL ANALYSIS PLAN

Expert statistical consultation will be obtained from the University of Auckland Statistical Consulting Centre. We intend to prospectively recruit 291 inpatient paediatric cases of acute appendicitis. This preliminary power calculation is based off our proof-of-concept study and assuming a=0.05, ß=0.1 and an enrolment ratio of 1:1.5 of rural to urban children.

Descriptive statistics will be used to describe basic demographics and distributions assessed for normality. Paired t -tests will be used to ascertain differences between continuous data assumed to be normally distributed, Wilcoxon–Mann– Whitney test used as a non-parametric analogue, chi-squared test for dichotomous variables and rank point-biserial correlation for ordinal variables.

No surgeon- or hospital-specific comparisons will be performed. Geographical analysis, travel distance calculation and geographic figures will be obtained using ArcGIS GIS Software Version 10.7.1. (ESRI Inc. Redlands, CA, USA).

Initial univariate analysis will be used to determine statistically significant variables, which after testing for multicollinearity will be used to create an ordinal regression model via backward elimination. Statistical analyses will be carried out using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). All tests will be two-sided and P -values of <0.05 considered statistically significant.

17 DATA COLLATION AND GOVERNANCE

Direct access will be granted to authorised representatives from the sponsor, data management team or host institution for monitoring and/or audit of the study to ensure compliance with regulations.

17.1 Data Recording and Record Keeping

Data management, security and training will be undertaken by the University of Auckland Central Coordinating Research Hub which is hosted by the Liggins Institute. Data are to be collected and stored online through a secure server running the Research Electronic Data Capture (REDCap) web application. REDCap allows collaborators to enter and store data in a secure system. It is widely used by academic institutions and all storage of web-based information by this system is encrypted with HIPAA-Security compliance guidelines in the United States.

Electronic databases will be stored on secure servers at the University of Auckland and access will be controlled by unique user ID and password, with full electronic tracking log. The screening database will record NHI, age, ethnicity, address and eligibility criteria of participants considered for enrolment. This will enable reporting of CONSORT data, assessment of external validity and to allow investigators to monitor if any particular groups are at risk of being underrepresented in our study. Collaborators will be given secure REDCap server login details, allowing secure data storage on the REDCap system. No patient identifiable information will be uploaded or stored on the REDCap database. All anonymous data will be held for a total of ten years, after which it will be permanently removed from the server space.

Following recruitment, trial data will be stored in a separate database with eCRFs labelled by a de-identified ID. To ensure we are not approaching a family twice, NHI and address will be stored in the screening database but **not** the trial database. Contact information will be stored in a separate database, independently of the trial database and will be accessible only to site coordinators and the coordinating investigator. Data Access Groups will be employed so that site personnel can only see data for participants at their site. Download of data will be restricted to the data manager, study coordinator, site investigators and primary investigator, and **only** the data manager and coordinating investigator will be able to download identifiable data.

Electronic data files will be stored in the REDCap trial database file repository providing the same secure, protected access as above. Any hard copy CRFs will be stored in a locked cabinet until scanned into the file repository and then destroyed.

At the completion of the study, all electronic data will be permanently digitally archived and accessible only to the study investigators. All hard copy records that have been digitally scanned will be added to the archive, and then destroyed. Remaining hard copy records will be stored in a locked cabinet in a secure office, and will be accessible only to the study investigators. Records will be retained for 10 years after the age of majority.

All centres must have confirmation of successful study registration prior to commencing data collection. REDCap accounts cannot be issued until evidence is received of successfully registration and locality assessment of the study at a centre.

17.2 Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. (In addition, the collaborator may discontinue a participant from the study at any time if the collaborator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Withdrawal of Consent or loss to follow up.

Depending on the stage of data processing, when a participant voices their wish to withdraw from the study, it may not be possible to destroy all records of the interview pertaining to that participant. The participant will be offered the choice between having any data that is identifiable as belonging to them removed or allowing it to continue to be used.

17.3 Definition of End of Study

The end of study is the completion of the 30 day follow up for the last patient recruited. This will be the 13th of June 2020.

18 ETHICAL AND REGULATORY CONSIDERATIONS

18.1 Declaration of Helsinki

The collaborator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

18.2 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted for Locality Assessment at each centre as well submitted for HDEC approval. The collaborator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

18.3 Reporting

The CI shall submit on completion, or on request, a progress report to the HDEC, host institution, sponsor or funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

18.4 Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all trial documents and the trial electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be de-identified as soon as it is practical to do so. In the setting of this study, this will occur upon recruitment where after screening has occurred, no identifiable data will be uploaded into our trial database.

19 FINANCE

19.1 Funding

Funding has been obtained from the Auckland Medical Research Foundation Doctoral Grant – reference number: 1219003.

Funding is not expected from any individual locality or District Health Board nor is this study expected to impinge on the resources and standard care provided by District Health Boards.

20 PUBLICATION POLICY

Site collaborators, consultant surgeons, local leads, national committee members & the study management group are eligible for PubMed-citable co-authorship. This will be in line with the RACS CTANZ authorship policy which will be distributed to the study team.

Some specific requirements exist: A maximum of three collaborators and one supervising consultant per site will be listed as 'PubMed' citable authors. Each site collaborator should participate in gaining local approval, identifying patients, collecting data and follow-up, ensuring >95% data completeness. Unfortunately, sites with >5% missing data will be excluded from the analysis and the contributing team will be removed from the authorship list.

21 DISSEMINATION & IMPACT:

The impact of the RURAL study will be measured using the following criteria:

- Presentation of local results to clinical teams and local research meetings
- Presentation of local results to Māori research services.
- Presentation of national results at the RACS ASC.
- Dissemination of results via professional bodies with audiences related to surgery or rural health.
- Dissemination of results in peer-reviewed journals
- Dissemination of results to patient and public interest groups

22 APPENDIX A: PAEDIATRIC APPENDICITIS SCORE

Note: This is automatically calculated by our data-entry tool.

Components of Paediatric Appendicitis Score[17]

Signs/Symptoms	Point Value
Nausea/emesis	1
Anorexia	1
Migration of Abdominal Pain to Right Lower Quadrant	1
Temperature ≥ 38 degrees Celsius	1
Right Lower Quadrant Tenderness on Light Palpation	2
Cough/percussion/heel tapping tenderness at Right Lower Quadrant	2
Leukocytosis as defined by WBC ≥10 ($x10^9$/L)	1
White Cell Left Shift as defined by Neutrophil Count ≥7.5 ($x10^9$/L)	1
Total	**10**

An electronic copy can be found at: https://www.mdcalc.com/pediatric-appendicitis-score-pas

23 APPENDIX B: REQUIRED DATA FIELDS

Demographic Data Points		
1	Age	[Years]
2	Gender	Male, Female, Other
3	Ethnicity (Screening off NHI)	NZ European, NZ Māori, NZ Pacific, Other
4	Deprivation Quintile	Q1, Q2, Q3, Q4, Q5
5	Time of Presentation to THIS ED	DD/MM/YY HH:MM
6	Statistics NZ Rurality Descriptor	Major Urban Area, Large Urban Area, Medium Urban Area, Small Urban Area, Rural Settlement, Rural Other
Prehospital Data Points		
7	Time elapsed from pain onset to presentation	[Hours]
8	Time elapsed from symptom onset to presentation (if pain not main symptom)	[Hours]
9	Was this a school/work day?	Yes,No
10	Main Presenting Symptom of Parent	Pain, vomiting, diarrhoea, anorexia, other
11	Travel Distance on Day of Presentation	[Kilometres]
12	Did Parent have to Take Time off Work?	Yes, No
13	Was this of consequence to the family?	Yes, No, Indifferent
14	Approximate household's total annual income?	[Income band]
15	Total number of dependent children	[Value]
16	Previous experience with appendicitis	Yes, No
17	Awareness of appendicitis	Yes, No
18	Presented to another health service before here?	Yes – Primary Care, Yes – Whitecross, Yes – Rural Hospital, Yes – Other, No
19	Health advice from others prior to presentation?	Yes, No (Who)
20	Method of Travel to THIS Hospital	Private – own transport, Private – borrowed transport, Ambulance, Helicopter, Public Transport, Other
21	Were you delayed in presenting today?	Yes, No
22	If so, by what?	Free text
23	What ethnicity do you belong to?	MoH Ethnicity Groups – can choose multiple.
Preoperative Clinical Data Points		
24	Transferred from another hospital pre-operatively?	Yes, No
25	If yes, method of transfer? Time & Date of Presentation to this Hospital	Ambulance, helicopter, private transport DD/MM/YY HH:MM
26	RLQ tenderness to cough, percussion or hopping	Yes, No
27	RIF tenderness to palpation	Yes, No
28	Migration of pain to the RLQ	Yes, No
29	Anorexia	Yes, No
30	Preoperative Fever ≥38.0	Yes, No
31	Pre-operative Tachycardia?	Yes, No
32	Pre-operative Hypotension?	Yes, No
33	Pre-operative IV fluid resuscitation?	Yes, No
34	Nausea or Vomiting	Yes, No
35	Did patient have pre-operative blood tests?	Yes, No
36	WBC ≥10×10^9 cells/L	Yes, No
37	Maximum Preoperative WBC	×10^9 cells/L
38	White Cell Left Shift (ANC ≥7.5)	Yes, No
39	Maximum Preoperative CRP	mg/L
40	Preoperative Serum Sodium Level	mmol/L
41	Paediatric Appendicitis Score	0-10
42	Preoperative IV Antibiotics Given?	Yes (& Which), No

43	Preoperative Imaging?	Yes, No
44	If yes, what imaging?	Ultrasound, MRI, CT, Other
45	Imaging Findings	Appendicitis, Equivocal, Negative
46	Appendiceal abscess on Imaging?	Yes/No
47	Pre-op clinical/radiologic diagnosis of perforation	Yes/No
48	Primary management	Operative, interventional radiology, conservative (why).
Operative Data Points		
49	Time Operation Started	DD/MM/YY HH:MM
50	Type of Operation (Knife to skin)	Laparoscopic, Laparoscopic Converted to Open, Open.
51	Macroscopic Appendicitis?	Yes, No
	If above no: No cause for pain identified intra-op?	Yes, No
52	Alternative/Incidental Finding explaining pain?	Ovarian, Meckel's, PID, Other
	Macroscopically Normal Appendix Removed?	Yes, No
53	If appendicitis: Macroscopic Gangrene?	Yes, No
54	Macroscopic Perforation?	Yes, No
55	Purulent Free Fluid?	Yes, No
56	Histologic Appendicitis?	Yes, No
57	Histologic Necrosis?	Yes, No
58	Faecalith (Macroscopic or Histologic)	Yes, No
59	AAST Appendicitis Grade	0, I, II, III, IV, V
60	Time of Discharge	DD/MM/YY HH:MM
61	Length of Stay	[Days]
Postoperative Complications		
62	Post-operative IV antibiotics give?	Yes (& which), No
63	Script given for antibiotics on DC?	Yes (& duration), No
64	Wound Infection?	Yes, No
65	Post-operative Ileus	Yes, No
66	Post-operative ICU or HDU Admission	Yes, No
67	Pneumonia	Yes, No
68	Intra-abdominal Collection	Yes, No
69	Re-operation	Yes, No
70	30-day Readmission	Yes, No
71	Highest Clavien-Dindo Grade	0, I, II, III, IV, V

24 APPENDIX C: PATIENT QUESTIONNAIRE

With the consent of the parent/caregiver and at a time convenient to them please record the answers to the following questions. Please consider importance of family/whanau support in shared decision making and offer to return at a time more suited to the family if need be. Italicised text is the suggested wording of the question.

"Appendicitis is an illness that progresses over time and often it's hard to know when to seek medical attention. It also rarely happens at a time that's convenient for families, which can mean time off work and school. We're interested in knowing how you picked up that your child was unwell, how you made it to hospital and if there is anything that could have made it easier.

Prehospital Symptom Onset: *"Appendicitis can start mildly and build up over time. How long did your child have symptoms before you arrived in hospital?"*					
Time and date of symptom onset: (If a symptom other than pain please also record when pain was reported/started)	__ : __ __/__/__ __ : __ __/__/__				
Was this a school/work day?	Yes/No				
What was the child's *main* symptom that worried you? (As reported by parent, not doctor: E.g. pain, fever, diarrhoea, vomiting)					
Financial Burden and Opportunity Cost: *"A family only has a limited amount of time and money. Having to take time off work or school can be a big deal for some or not so much of an issue for others."*					
Did you or a caregiver in your household have to take time off work to bring your child to hospital?	Yes/No				
If so, did this make it hard for your household to get by? *(Yes, no, indifferent/not really)*	Yes/No/Not Particularly				
Approximately, what is your household's total annual income?	$20,000 or less	☐	$70,001-$100,000	☐	
	$20,001 - $30,000	☐	Over $100,001	☐	
	$30,001-$50,000	☐	Prefer not to say	☐	
How many children do you usually look after on a day-to-day basis?	Number:				
Disease Recognition and Health-Seeking Behaviour: *"Appendicitis is common but not everyone knows about it. Before it gets bad enough to go to hospital, some families get advice from friends, family or health staff in the community"*					
Aside from your child, have you or anyone you know had appendicitis?	Yes/No				
Before your child's illness, did you know what appendicitis was and what to look out for?	Yes/No/Not Really				
Were you seen by another health service before arriving here? *For example your GP, community nurse, urgent care…*	Yes/No (Clarify who)				
Did you seek advice from friends, family or the internet regarding your child's illness before arriving to hospital?	Yes/No (Clarify who)				
Who made the decision to come to hospital? (E.g. Mum, dad, joint parental, friend, family member, health professional)					
Transport and Parent Impression of Delay: *"Once the decision was made to come to hospital, it's easier for some families to get here than others. Some live further away and not everyone has reliable access to a car"*					
How did your child get to hospital? (E.g. Private car (own), private car (borrowed), driven by friend or family member not you, public transport, ambulance, helicopter…)					
Did you get to hospital as quickly as you would have liked?	Yes/No				
If not, what was the main thing that delayed you? Free text – E.g: *No available transport, work, having to organise other children, waiting at another health care service…*					
Self-Reported Ethnicity*					
Which ethnic group do you belong to? (May pick more than one)	NZ European	☐	Cook Island Māori	☐	
	Māori	☐	Tongan	☐	
	Samoan	☐	Niuean	☐	
	Chinese	☐	Indian	☐	
	Other:				

*As NHI data can under-represent Māori by 20%

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26 AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
0	1.0	28/06/2019	Dr Brodie Elliott	First Draft of Protocol
1	1.1	23/08/2019	Dr Brodie Elliott	Amendments + corrections made after peer review from Professor Bissett.
2	1.2	26/09/2019	Dr Brodie Elliott	Amendments post Southern HDEC review.
3	1.3	27/10/2019	Dr Brodie Elliott	Amendments after review by Professor Beasley
4	1.4	21/11/2019	Dr Brodie Elliott	Amendments after recommendations by HDEC Northern B review.