NAVKIDS^2 trial: A multicenter, waitlisted, randomised controlled trial of patient navigators in children with chronic kidney disease

Protocol Number (18.01)
Version: 9.0
Date: 06/12/2021

Trial Registration
Australian New Zealand Clinical Trials Registry ACTRN 12618001152213

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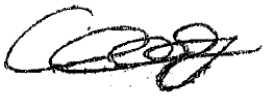
Protocol Sign Off	
Sign off date	06 Sep 2019
Current version sign off	06 December 2021 (version 9.0)

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Sponsor/s:
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Statement of Compliance

This document is a protocol for a research project. This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

Site Principal Investigator Agreement

The following statements refer to the current and future approved versions of the NAVKIDS[2] trial protocol.

- I agree the Intellectual Property contained within this protocol belongs to The University of Queensland and that the protocol will only be used, distributed or discussed in the context of conducting of the NAVKIDS[2] trial.
- I have read this protocol and agree that it contains all necessary details for carrying out the study as described.
- I will conduct this protocol as outlined herein, including all statements regarding confidentiality.
- I will make all reasonable efforts to complete the study within the time designated.
- I will provide copies of the protocol and all information provided by the Trial Steering Committee (TSC) or the Australasian Kidney Trials Network representative to site study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the study.
- I understand that the study may be terminated or enrolment suspended at any time by the TSC, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.
- I agree to conduct this study in full accordance with all applicable regulations and the principles of the International Conference on Harmonization guidelines on Good Clinical Practice (ICH GCP).

Site Principal Investigator Name: _____

Site Principal Investigator Signature: _____

Date signed: _____

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1. GLOSSARY OF ABBREVIATIONS & TERMS

Abbreviation	Description (using lay language)
AIHW	Australia Institute Health and Welfare
AKTN	Australasian Kidney Trials Network
ANZDATA	Australia and New Zealand Dialysis and Transplant
CKD	Chronic kidney disease
CKD-D	Chronic kidney disease on dialysis
CKD-T	Chronic kidney disease with a transplant
CV	Cardiovascular
CVD	Cardiovascular disease
DRG	Diagnosis-related group
eGFR	Estimated glomerular filtration rate
HREC	Human Research Ethics Committee
HRQoL	Health Related Quality of Life
HUI	Health Utility Index
KCAD	Kids with CKD study
LV	Left ventricular
LVH	Left ventricular hypertrophy
MBS	Medicare Benefits Schedule
NDI	National Death Index
OR	Odds ratio
PBS	Pharmaceutical Benefits Scheme
PedsQL™	Pediatric Quality of Life Inventory™
PISCF	Patient Information Sheet and Consent Form
QALYs	Quality Adjusted Life Years
RA	Remoteness Areas
REDCap	Research Electronic Data Capture
SAP	Statistical Analysis Plan
SES	Socioeconomic status
SRH	Self-rated health
SMC	Safety Monitoring Committee
TSC	Trial Steering Committee
URG	Urgency-related group
WHO	World Health Organisation

2. STUDY SITES

2.1 STUDY LOCATION/S

Participants will be recruited from sites across Australia.

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The Children's Hospital at Westmead	Cnr Hawkesbury Road and Hainsworth Street, Westmead, NSW 2145	Dr Hugh McCarthy (Principal Investigator Westmead)	(02) 98451473	hugh.mccarthy@health.nsw.gov.au
Sydney Children's Hospital, Randwick	High Street, Randwick, NSW, 2031	Dr Sean Kennedy (Principal Investigator Randwick)	(02) 93821646	Sean.Kennedy1@health.nsw.gov.au
Queensland Children's Hospital, Brisbane	501 Stanley Street, South Brisbane, QLD, 4101	Dr Anna Francis (Principal Investigator Brisbane)	(07) 3068 5857	Anna.Francis@health.qld.gov.au
Royal Children's Hospital Melbourne	50 Flemington Road, Parkville, VIC, 3152	Dr Simon Carter (Principal Investigator Melbourne)	(03) 93459164	Simon.Carter@rch.org.au
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3. FUNDING AND RESOURCES

3.1 SOURCE/S OF FUNDING

National Health and Medical Council Medical Research Future Fund Rare Cancers, Rare Diseases and Unmet Need Initiative - APP1170021 (CIA Wong)

4. INTRODUCTION/BACKGROUND INFORMATION

4.1 LAY SUMMARY

The NAVKIDS[2] trial is a multicentre, waitlisted, randomised, controlled trial that assesses the health benefits and costs of a patient navigator program in children with chronic kidney disease (CKD) stages 1-5, on dialysis (CKD-D) and with kidney transplants (CKD-T) and of low socioeconomic backgrounds and/or living in rural/remote areas. Patient navigators are trained non-medical personnel who assist patients with complex and/or chronic conditions as they journey through the continuum of care and transit across different care settings. They help vulnerable and disadvantaged populations with chronic illness to better understand their diagnoses, treatment options, and available resources, to guide them through the very complex medical system and to overcome barriers to health care access and bridge gaps in transitions of care[1]. Given the complexity and chronicity of the disease process and growing concerns that current models of care in paediatric nephrology may not be equipped to support the provision of high level care in children with CKD from socio-economically disadvantaged backgrounds[2], a patient-navigation program may lead to improvement in the provision of care and overall health of children with CKD and may be cost-effective.

4.2 INTRODUCTION

The **NAVKIDS[2] trial is a multi-centre, waitlisted, randomised, controlled trial that assesses the health benefits and costs of a patient navigator program in children with chronic kidney disease (CKD) stages 1-5, on dialysis (CKD-D) and with kidney transplants (CKD-T), who are disadvantaged with low socioeconomic backgrounds and/or living in rural/remote areas.** The trial design and research plan are informed by the extensive longitudinal observational and qualitative data generated by the Chief Investigators (CIs) (Wong, Teixeira-Pinto, Howell, Caldwell, McCarthy) and Associate Investigators (AI) (Tong, Craig, Alexander, Howard, McTaggart, Walker and Mackie) of the **Kids with CKD (KCAD) study[3].** The KCAD study, a multi-centre, prospective cohort study of children with CKD (n = 377), has informed the: 1. Study design, 2. Inclusion criteria, 3. Intervention of choice and 4. Choice of outcomes measures of the NAVKIDS[2] trial. At least 50% of the participants from the KCAD study will satisfy the inclusion criteria for the NAVKIDS[2] trial. Recruitment is therefore highly feasible as we will be able to fulfil 90% of our sample size by inviting participants from the KCAD study alone.

CKD is a devastating illness associated with increased mortality, reduced quality of life, impaired growth, neurocognitive impairment and psychosocial maladjustment in children. The overall annual mortality rate for children on dialysis is 35 per 1000 population and is thirty-fold higher than children without CKD[4]. Such large discrepancies in mortality rates remain unchanged despite medical advances over the past two decades.

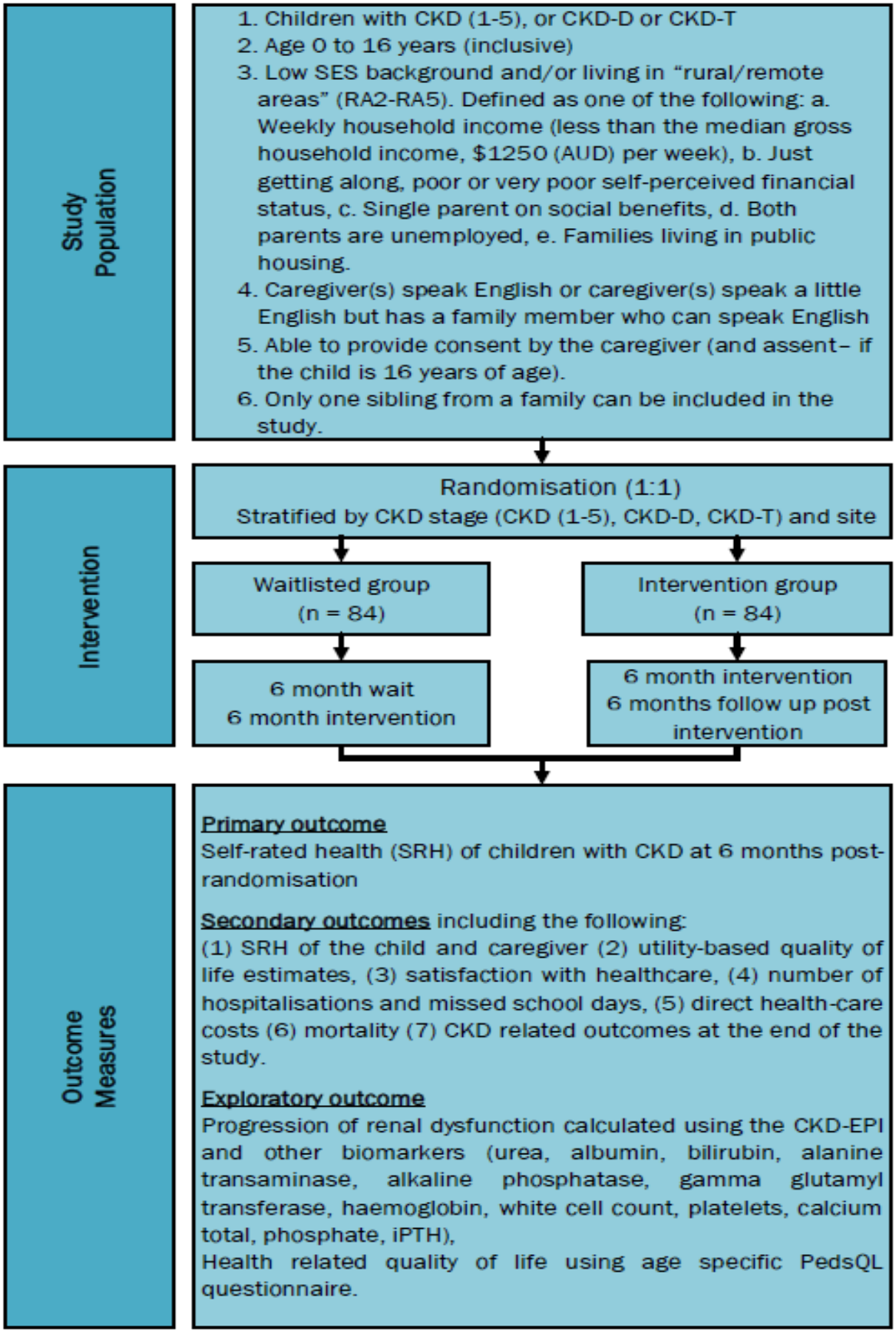
The key findings of the KCAD study indicated that poor health in children with CKD is not only attributed to the direct influence of the chronic illness but also reflects outcomes of the complex pathway that defines equitable access to healthcare. **We found that children with CKD of the lowest and second lowest socioeconomic status (SES) quartiles were at least 3 and 2 times more likely to experience poorer overall health compared to the highest SES quartile[2].** Our work has also demonstrated the disparities in health among children with CKD are attributed to a myriad of different

barriers including patient-level, health system and provider factors that extend beyond the biological differences[5]. System level factors may include the inherent complexity of the health care system and poor access to primary or specialty care. At the provider level, barriers may include the lack of support systems to implement recommended care. Patient level barriers may include lack of awareness of resources, financial constraints, and competing priorities (e.g. family and work, and care for other siblings), that in turn make following complex care plans in the management of a child with CKD particularly challenging[6].

Our previous research has indicated that children with kidney failure living in remote/regional Australia are less likely to access optimal care including pre-emptive living donor kidney transplantation[43]. As such, there is a need to test novel interventions such as a community/patient navigator program that may improve such disparities in disadvantaged populations.

Patient navigators are trained non-medical personnel who assist patients with complex and/or chronic conditions journey through the continuum of care and transit across different care settings. They help vulnerable and disadvantaged populations with chronic illness to better understand their diagnoses, treatment options, and available resources, to guide them through the very complex medical system and to overcome barriers to health care access and bridge gaps in transitions of care[1]. In the context of cancer care, patient navigator programs improve patients' satisfaction with care and treatment adherence through overcoming modifiable barriers to achieve optimal health outcomes[7]. Outside oncology, there is evidence supporting application of patient navigator programs in children with chronic conditions, such as diabetes, asthma and obesity, for improved access to care[8-10]. Given the complexity and chronicity of the disease process and growing concerns that current models of care in paediatric nephrology may not be equipped to support the provision of high level care to children with CKD from socio-economically disadvantaged backgrounds[2], **we hypothesise that a patient-navigation program will lead to improvement in the provision of care and overall health of children with CKD and is cost-effective.**

4.2.1. Study Schema



4.3 BACKGROUND INFORMATION

CKD is a devastating condition in children: CKD is a progressive, systemic, multi-organ disease**.** Children and adolescents with CKD are at risk of dying prematurely. The mortality rate of children with CKD is at least 30-fold higher than their age-matched peers, and health outcomes are not improving. Children with CKD suffer from a diverse range of co-existing illnesses including cardiovascular disease (CVD), hypertension, neurocognitive impairment, mineral and bone disorders and impaired growth[11-14].

CVD is the number one cause of death in children with CKD, 40-50% of all childhood deaths are related to cardiovascular causes[15]. Early cardiovascular abnormalities, including left ventricular hypertrophy (LVH) and LV dysfunction, damage to the large arteries such as stiffness and increased intima-medial thickness of the carotids, and coronary calcification, are highly prevalent in these children[11].

Neurocognitive functioning and academic achievement*:* CKD also negatively impacts on the neurocognitive and emotional health of the child. CKD has a profound influence on brain development, including cortical atrophy, cerebral infarcts and micro-vascular disease. As part of the KCAD study and a recent systematic review conducted by the investigator team, we have shown that children with CKD have lower intellectual functioning compared with the general population, with deficits across academic skills, particularly in mathematics and spelling, executive function, and both visual and verbal memory[16].

Poor nutrition and impaired growth: Growth failure is inextricably linked with CKD. Growth failure in the setting of kidney disease is multifactorial and is related largely to poor nutritional status, as well as comorbidities, including anaemia, bone and mineral disorders, alterations in hormonal responses, and other aspects of treatment side effects, such as steroid use.

Health related quality of life (HRQoL): As the severity of CKD worsens, there is a subsequent decline in the overall HRQoL of the child and increased use of health care resources, as well as burgeoning costs. Data from our KCAD study found that children and adolescents with CKD experience significant deficits in overall and domain-specific QoL, particularly for children on dialysis[17] (**Figure 1**).

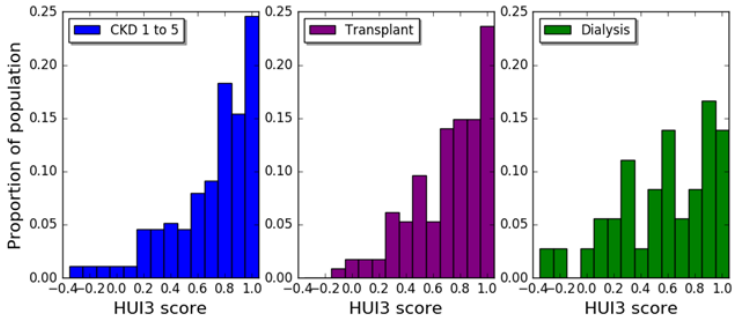


Figure 1. Distribution of quality of life score by stage of CKD

Psychosocial impact of CKD: In addition to the biological impact of the disease, the lives of children with CKD may also be affected in many other ways. Children with CKD may have a negative self-image and have relationship problems with family members due to the stress of living with a chronic disease. The condition may lead to behaviour problems and make participating in school and extracurricular activities more difficult. Children with kidney failure may miss school each week because of dialysis and medical appointments. These absences can compound the learning problems many children with CKD face.

Overall health status of children with CKD: Self-rated health (SRH) is a recognised and validated measure of overall health. It can be used to predict mortality in children with chronic illnesses[18] and is commonly used as a measure of overall health status in population surveys[19]. The SRH of the child is a reliable indicator of the underlying health state and disease burden experienced by the patient.

Data from the KCAD study indicated approximately 25-40% of child rated health as fair or poor, with children on dialysis and those with comorbidities reporting the worst overall health[2].

Caregiver burden for children with CKD: Children with CKD depend on their parents and caregivers for multifaceted, continuous and intensive support. Because of the complexity of the illnesses, diagnosis, treatment and care of the child with CKD often involves a multi-modality and multidisciplinary management approach with input and expertise from different specialties. The child may need complicated medication regimens, such as immunosuppression therapy after transplantation, or be required to follow a specific diet in the context of on-going dialysis treatment. It is critical that they follow their health care provider's recommendations to help control their disease. As such, the role of the caregiver can be stressful, exhausting and overwhelming, particularly when faced with invasive interventions, such as 'needling the fistula'. Often, the diagnosis of CKD disrupts the family dynamics, and can have significant impacts on the home environment, finances and recreation. In many cases, siblings feel neglected and abandoned because the sole focus is on the child who is ill, and parents may experience marital tension and conflict, fuelled by guilt, blame and financial stress. One of the key gaps highlighted in our qualitative work *suggested better support networks and structures* are needed to help families to cope with psychological and physical difficulties encountered during all stages of their child's illness[20,21].

The economic and financial burden of having CKD: Baseline data from the KCAD study shows that 20% of parents are single parents and 41% are unemployed. Less than 30% of the primary caregivers have completed a bachelor's degree or higher tertiary education and >40% of the participants live in shared facilities[2]. Social and financial inequalities are most pronounced in children with end-stage kidney disease. Our data have shown that parents of children on dialysis are twice as likely to be unemployed as parents of children with either pre-end stage kidney disease or who had a kidney transplant. Caregivers of children on dialysis are at least two-times more likely to be in the lower income category and have lower perceived financial status than caregivers whose children are not on dialysis. Our qualitative data also highlight caregivers' financial difficulties in the coverage of medication, transport, childcare costs, and the lack of workforce participation in the context of chronic disease and the high burden of clinical care they shoulder[22]. Due to the technical complexities and time-consuming nature of dialysis procedures, such as administering medications, many parents view caring for a child with CKD as prohibitive to sustaining employment[5].

SES is a key driver of health disparities in children with CKD: A strong social gradient exists in children with chronic disease, with more deprived groups having a higher prevalence of disease and poorer outcomes[23,24]. In children with CKD, our data from the KCAD study indicate a significant impact of socioeconomic inequality on overall SRH of the child. Children whose caregivers are unemployed, with below median weekly incomes, poor perceived financial statuses and lack of home ownership are at least 3-times more likely to experience fair to poor health compared to children with caregivers who are more affluent[2].

More importantly, we have shown the link between SES and health outcomes in children with CKD are multidimensional. The key and novel findings indicated that at least 20% of the effects observed between SES and poor health are mediated by the health and well-being of the caregivers/parents, suggesting the effects may lie directly in the causal pathway between low SES and health in children with CKD. Therefore, interventions that work on improving the overall well-being and quality of life of the caregivers may have a significant impact on the overall health of the child.

Potential role of patient navigators in children with CKD: Patient navigators are trained non-medical personnel who assist patients with complex and/or chronic conditions as they journey through the continuum of care and transit across different care settings. A patient navigator is an intervention that

addresses the disparities in health among medically underserved populations. Patient navigator programs for cancer-related care have been implemented across the United States for the last 30 years to enhance access to care and services in underserved populations. Among the many interventions to address these barriers to clinical care, patient navigation has specifically shown promise and is now incorporated into some guidelines for clinical care[25]. **The roles of the patient navigators are diverse, but they have the key objectives of facilitating patients' receipt and access to care to improve the overall health of patients from low SES backgrounds and/or living in rural/remote areas.** Patient navigators use the care management model[26] to identify barriers and to recommend care, develop strategies to address these barriers and track patients through the steps in medical evaluation and treatment. In the context of children with CKD, their responsibilities may include helping patients to keep track of appointments, particularly when the organisational and executive skills of the child are affected, provide social support, interpret health information provided by the clinicians and facilitate communication within the families when parents are separated. Patient navigators may help patients forge a more participatory dialogue with their clinicians, and guiding the patients to ask the right questions, enhancing patient autonomy. Patient navigators can also provide support for caregivers; e.g. managing transport to and from the hospital or coping with the complex organisational network within the hospital, particularly for those of lower literacy, low SES and families from non-English speaking backgrounds**.**

Evidence of benefits: Observational and randomised controlled studies have examined the impact of a patient navigator program in adult cancer care and have shown increased uptakes of cancer screening, improved timeliness in follow-up, improved patient satisfaction, and timely treatment of cancer after initial diagnosis, particularly among the most vulnerable[27,28]. A Cochrane review of 17 trials reported that the benefits for people with chronic disease of a navigator program included significant improvements in psychosocial well-being, self-rated general health, and domain-specific quality of life, such as pain, disability and fatigue[29]. In children, evidence supporting the benefits and effectiveness of a patient navigator program is limited to observational studies and trials of small sample size. A systematic review of 17 studies in children with chronic diseases, including diabetes, asthma, and obesity, and from low SES found some benefits in overall health status, symptom control, improved parental quality of life, and reduction in missed school days and missed parental work days[30]. A more recent review of 54 RCTs (none in children with CKD) indicated some positive effects on patient reported outcomes, particularly for improving the process of care and overall health in patients with chronic disease[31].

The need to study the impact of a patient navigation program in children with CKD and of low SES: Data from our KCAD observational and qualitative studies indicated that substantial system, provider, and patient-level barriers to care exist, particularly among families with low SES. Further, our data suggest that these institutional and systemic barriers can contribute directly to the observed poor overall health of the child. Despite understanding the health gaps in children with CKD and how they may be intricately related to SES, there are currently no effective actions and initiatives to address this disparity. The NAVKIDS[2] trial will allow evaluation of the effectiveness of a patient navigator program on the timeliness of access to care and treatment, and on patients' and caregivers' satisfaction with care, quality of life and the overall health and well-being, which in turn may help to close the gap in health disparities across the social gradient.

5. STUDY OBJECTIVES

5.1 RESEARCH QUESTION

In children with CKD (1-5), CKD-D and CKD-T who have low SES backgrounds and/or living in rural/remote areas, does a patient navigator program improve self-rated health at 6 months post-randomisation compared to standard care?

5.2 PRIMARY OBJECTIVES

To compare the self-rated health (SRH) of children with CKD randomised to the intervention (patient navigator program) and the waitlisted control arms.

5.3 SECONDARY OBJECTIVES

To compare the secondary end-points between groups including utility-based quality of life, SRH of the caregiver, caregivers' satisfaction with healthcare, progression of kidney dysfunction, other biomarkers, the number of hospitalisations and missed school days, and mortality and assess the cost-effectiveness of a patient navigator program in children with CKD.

Additionally, to assess the fidelity, satisfaction, and barriers of a patient navigator program in children with CKD.

5.4 OUTCOME MEASURES

The primary study end-point is SRH of the child 6 months post-randomisation. ***Justification for the primary outcome:*** SRH, a patient-reported health outcome, is a validated composite measure of the children's global health status, including both physical and quality of life construct[32]. It is a holistic measure that accommodates the World Health Organisation (WHO) defined concept of health. SRH is also a stable measure of health over time[32]. Prior studies have shown that children (from age 8 onwards) can accurately communicate their health symptoms in a meaningful way and can provide valuable insights into their own health[33]. Below the age of 8, children may have difficulties in interpreting and understanding the response categories. As such, parent-rated health of the child will be used as a proxy for children between ages 0-7. Parent-rated health has been validated for use in young children (as young as 8 weeks old)[34,35]. Recent work also indicated that parental rating of the child's overall health is a sensitive measure when validated against the child's chronic conditions, comorbidities and mortality[18,36].

The key secondary end-points are the SRH of the child over time, SRH of the caregiver, utility-based quality of life estimates, caregiver satisfaction with healthcare, the numbers of hospitalisations and missed school days using diary card (for those attending school). Other secondary endpoints include direct health-care costs, mortality, and CKD-related outcomes for CKD-D and CKD-T patients, up to 12 months post-randomisation. *Utility-based quality of life* will be assessed using the Health Utility Index (HUI-3) for children aged 3 and above due to practicality (some questions are difficult to answer for very young children). Although the HUI has been used for young children in previous studies, it has only been validated for children aged 5 and above, therefore a sensitivity analysis will be conducted excluding children aged 3-4 years[37-40]. *Caregiver satisfaction with healthcare:* Caregivers will be asked to complete a survey on their satisfaction with the healthcare their child receives covering issues such as perceived access to care and confidence in navigating the healthcare system. *School absenteeism:* Caregivers will be asked to report on number of days child was absent from school. *All-cause, cardiovascular (CV) and other cause-specific mortality:* All-cause, CV and non-CV related mortality will be obtained at 12 months post-randomisation using data linkage with the National Death Index (NDI), housed within the Australia Institute and Health and Welfare (AIHW). CKD-related outcomes among those on dialysis and with kidney transplants will be obtained via linkage (at 12 months post-

randomisation) with the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry. All data linkage will be performed once all patients have completed 12 months follow-up and data will be collected for the 12 months the participant is in the study from the time of randomisation (i.e. the start of the study). *Direct healthcare costs and resource use:* Healthcare resource use will be estimated using hospitalisations information (parent-reported and medical records) and linked Medicare Australia data for outpatient healthcare use ((Pharmaceutical Benefits Scheme (PBS) and Medicare Benefits Schedule (MBS)). Cost will be estimated by applying diagnosis-related group (DRG), urgency-related group (URG) or Medicare unit costs and will also include the costs of the patient navigator program. Healthcare cost outcomes will be calculated for the following time points: 3 months into treatment, immediately post-treatment in both groups and at 6 months post-treatment in the immediate group.

Exploratory endpoints

Progression of kidney dysfunction calculated using a modified Schwartz equation for the estimated glomerular filtration rate (eGFR), and other biomarkers (urea, albumin, bilirubin, alanine transaminase, alkaline phosphatase, gamma glutamyl transferase, calcium total, phosphate, intact parathyroid hormone, haemoglobin, white cell count, platelets) at 6 months post-randomisation.

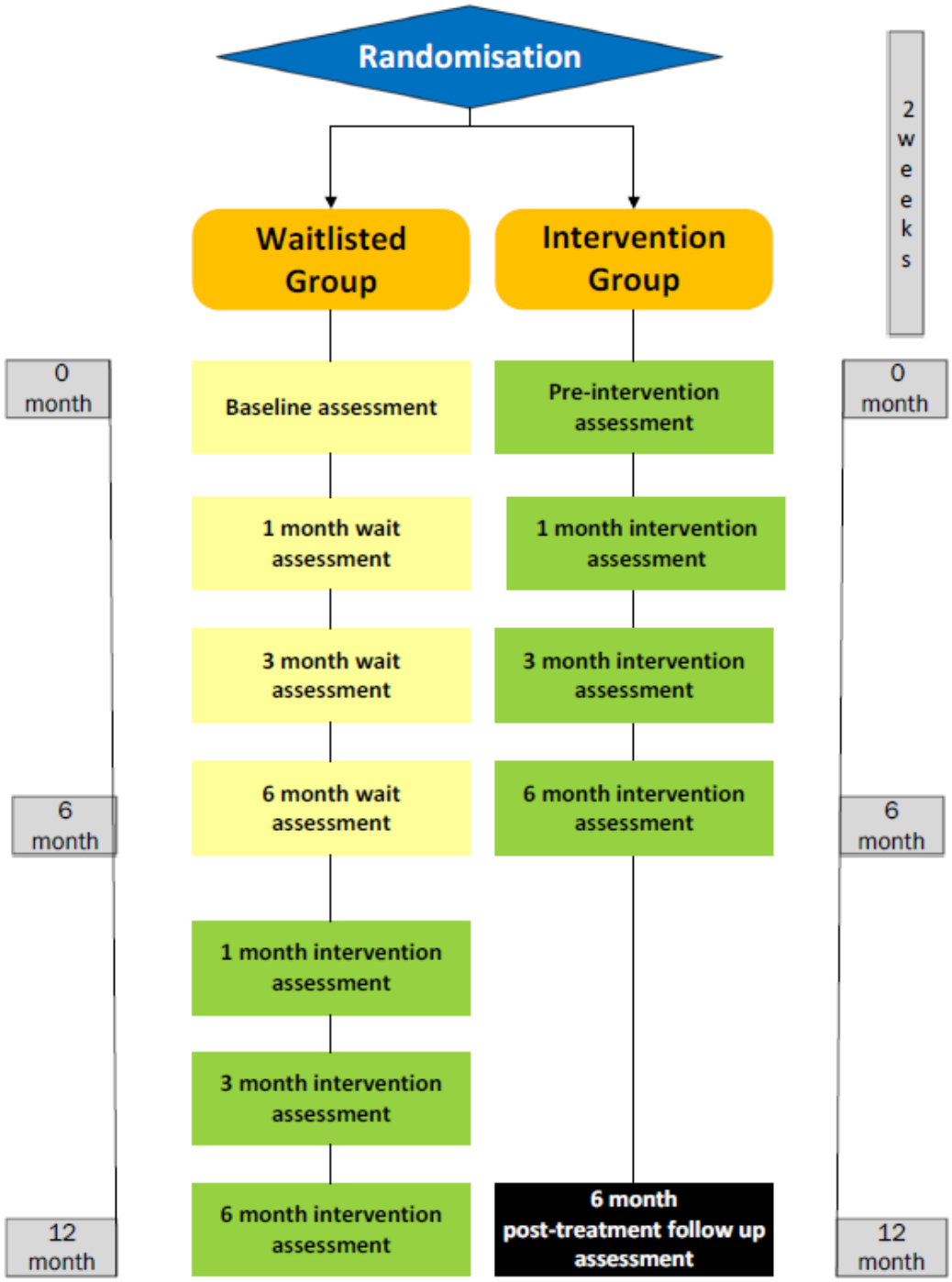
In collaboration with National Health and Medical Council Medical Research Future Fund Targeted Health System and Community Organization Research – APP 1199902 Tools for Outcomes Research to Measure and Value Child Health (CIs Howard, Howell, Wong and Craig) (TORCH) project, exploratory measures of health-related quality of life will be included for a subset of trial participants. The Pediatric Quality of Life Inventory (PedsQL™)[44] will be used to obtain QoL measures for all age groups[44].

Justification for the exploratory endpoints. PedsQL is the most widely used paediatric health related quality of life measure with specific versions for a range of age groups in children older than 1 month. Unlike HUI, it is a non-utility based instrument, however, a descriptive analysis has been developed that is amenable to valuation and generation of utility values. NAVKIDS will enable two important aspects relevant to developing evidence for the evaluation of child health by the TORCH project. Firstly, head to head comparative analysis with HUI-3 using longitudinal data will contribute to evidence for the strengths and weaknesses of HUI. Secondly, the comparative data will provide evidence on the merits of the TORCH program developing an Australian valuation of PedsQL thereby providing Australian decision makers with robust evidence of the health and quality of life in Australian children. Inclusion of the PedsQL infants measure will have important benefits for both NAVKIDS2 and the TORCH program. Currently there is a paucity of measures for the health of infants. This fills a current gap in the NAVKIDS2 assessment of health in infants not covered by HUI. Furthermore, the head to head comparison with parent-proxy SRH will add to the evidence of the strengths and weaknesses of PedsQL. PedsQL takes less than 5 minutes to complete and will be a minimal extra burden for the selected participants. *Creatinine and other biomarkers* (urea, albumin, bilirubin, alanine transaminase, alkaline phosphatase, gamma glutamyl transferase, calcium total, phosphate, intact parathyroid hormone, haemoglobin, white cell count, platelets) will be measured from blood samples.

6. Study Design

6.1 Study Design Diagram

Figure 2 Study design diagram



6.2 STUDY TYPE & DESIGN & SCHEDULE

The NAVKIDS[2] trial is a multicentre, waitlisted, randomised, controlled trial of patient navigators in children with CKD.

Justification of the study design: There is some evidence of health and social benefits, and a general belief that the patient navigation program will do more good than harm in children with chronic illness. As such, it would also be unethical to withhold the intervention from a proportion of the participants as in a traditional parallel design. The waitlist, controlled design has the benefit of allowing **all eligible participants** to be enrolled and **receive the same intervention for the same duration of time, but waitlisted entry allows participants with waitlist entry to serve as controls.**

Specifically, to be eligible for the study, participants must satisfy all of the criteria below:

1. Children with CKD (1-5), or CKD-D or CKD-T
2. Aged 0 - 16 years (inclusive)
3. Low SES background and/or living in "rural/remote areas" (RA2-RA5). Low SES families are defined as one of the following (self-reported):
   a. Weekly household income (less than the median gross household income, $1250 (AUD) per week),
   b. Just getting along, poor or very poor self-perceived financial status,
   c. Single parenting on social benefits,
   d. Both parents are unemployed,
   e. Families living in public housing.
4. Caregiver(s) speak English or caregiver(s) speak a little English but has a family member who can speak English
5. Able to provide consent by the caregiver (and assent– if the child is 16 years of age).
6. Only one sibling from a family can be included in the study

Currently, a total of 194 children within the KCAD cohort are from low SES backgrounds.

The patient navigator will work with patients, caregivers and health professionals to achieve better care and health through involvement in the social, community and health organisational network. It is a complex intervention and will be individualised, tailored to the needs of the patients and families[41]. The patient navigator will follow a *four-by-four matrix of tasks and networks plan*:

1. *Identification of task categories for a specific patient and family*: navigating tasks may consist of identifying and mitigating barriers with patients and healthcare professionals. They may include telling (explaining where and when a kidney biopsy will be done), inquiring (asking about the potential barriers, such as language barriers to attend the next appointment after the biopsy), supporting (listening to the fears about the interventions) and coaching (discussing the potential questions the patients and families may wish to ask in the next appointment).
2. *Facilitation for a specific patient and families*: the patient navigator may coordinate communication, seek advice from non-medical and medical staff and help to bring patients in for the appointments.
3. *Identification of networks*: the patient navigators will identify all potential network interactions that are relevant to the patients and their families. These may include: the health service providers, the non-clinical staff (administrators and receptionist), and other social support services such as the social workers, community-based services, transportation, and the maintenance of activities and system tasks for patients.

4. *Document and review*: the patient navigator will record their own actions (for example: steps taken with or on behalf of the patients and record other activities that are relevant to the patient navigator role).

Table 1. The specific role identified below will be recorded by the patient navigator for each patient.

	Task/network	Patient	Provider	Non-clinical staff	Supportive services
A	Identification of task				
B	Facilitation of task				
C	Identification of networks				
D	Document and review				

Table 1 Patient Navigator Data Collection Form

Participants who do not speak English and who also do not have caregivers/family members who speak English will be excluded from the study for feasibility reasons. Families with basic knowledge of English who can be assisted by English speaking children or other family members can be included in the study. This level of communication will be sufficient for the navigator assisting participants with day-to-day navigation activities. These families will have access to a phone interpreter service during consent and study visits for data collection. The key study information sheet will be translated to some of the most commonly used language other than English. In terms of available times, the patient navigator will be available to families during business hours on weekdays. In terms of time per week, considering their overall caseload, we expect that the patient navigator will be available approximately 1 hour per week per family. However, this may vary in accordance to the needs of the individual patient and will be informed by data from the qualitative in-depth interviews at 1 months post intervention.

6.3 Standard Care and Additional to Standard Care Procedures

Routine blood tests will be conducted as per usual clinical care. In a number of instances, tests may not be taken during usual care and are required for the study, in which case, the participant may be asked to attend an additional pathology visit, either at their treating hospital, or if more convenient, their local pathology centre.

6.4 Randomisation

Individuals who meet the inclusion criteria (see 7.2) and have given informed written or verbal consent will be randomised with equal probability to the intervention or the waitlisted controlled group, via an independent central web-based system. The randomisation sequence is generated by a computerised random number generator, using a random permuted block design with randomly chosen block sizes. Randomisation will be stratified by CKD stage (CKD (1-5), CKD-D, CKD-T) and site. Then permuted block will be used for each stratum (combination of CKD stage and site). It is anticipated that up to 21 children will be randomised to the intervention and waitlisted arms at each site (42 children in total for each site). Children randomised to the intervention arm will receive the intervention (patient navigator program) immediately after randomisation for 6 months. Assessments (including the SRH of the child, utility-based quality of life, caregiver satisfaction with healthcare, the number of missed school days) will be conducted pre-intervention, 1-month and 3-months into the intervention, immediately post-intervention and 6-months after the intervention. Children

randomised to the waitlist arm will wait for 6 months, but receive the standard care during the 'wait-period' and commence the intervention (patient navigator program) after 6 months. Assessments during the 'wait-period' will be conducted at baseline, 1-month and 3-months after randomisation and immediately pre-intervention, 1-month and 3-months into the intervention and immediately post-intervention. Similar to the intervention arm, the waitlist-controlled arm will receive the same intervention for a period of 6 months.

6.5 DATA COLLECTION SCHEDULE

The timing for all assessments is displayed in Table 2 (for the immediate treatment group) and Table 3 (for the waitlisted group).

For ease of reading all the visits that are conducted at 4 weeks (Visit 2), 12 weeks (Visit 3), 24 weeks (Visit 4), etc. are being referred to as months. The intervention is referred to as "6 months" in duration, however, the intervention and primary data collection are scheduled for 24 weeks with a window of ± 2 weeks.

Table 2. Schedule of assessments for immediate treatment group

	Screen	Randomisation	Treat (1 month)	Treat (3 months)	End treat (6 months)	Post-treat (6 months)
Visit Number		**1**	**2**	**3**	**4**	**5**
Day		**0 (Visit 1 within 2 weeks of rand)**	**28 +/- 2 weeks**	**84 +/- 2 weeks**	**168 +/- 2 weeks**	**336 +/- 2 weeks**
Eligibility Criteria	x					
Demographics		x				
CKD Information		x	x	x	x	x
Medical History		x	x	x	x	x
Physical Examination**		x	x	x	x	x
Bloods**		x			x	x
Immunosuppressive Medications		x			x	
Concomitant Medications		x			x	
SRH (Child and Caregiver)		x	x	x	x	x
Educational Background		x				
School Absenteeism		x	x	x	x	x
HUI Questionnaire*		x	x	x	x	x
Caregiver Satisfaction Questionnaire (Caregiver)		x	x	x	x	x
Patient Navigator Satisfaction Questionnaire (Caregiver)			x	x	x	
Events of interest			x	x	x	x
Hospitalisation			x	x	x	x
Data linkage (NDI, ANZDATA, MBS, PBS)						x
Qualitative Interviews/Questionnaires (subset of participants only)		x			x	
PedsQL**		x	x	x	x	x

mo = months

*HUI only to be completed by participants aged 3 years and above.

** Physical examination and blood test are not mandatory

****PedsQL completed only by some participants.** PedsQL for ages 1 month and above.

Table 3. Schedule of assessments for waitlisted group

	Screen	Randomisation	Wait (1mo)	Wait (3mo)	Start treat	Treat (1mo)	Treat (3mo)	End treat (6mo)
Visit Number		**1 (Visit 1 within 2 weeks of rand)**	**2 +/- 2 weeks**	**3 +/- 2 weeks**	**4 +/- 2 weeks**	**5 +/- 2 weeks**	**6 +/- 2 weeks**	**7 +/- 2 weeks**
Day		**0**	**28**	**84**	**168**	**196**	**252**	**336**
Eligibility Criteria	x							
Demographics		x						
CKD Information		x	x	x	x	x	x	x
Medical History		x	x	x	x	x	x	x
Physical Examination**		x	x	x	x	x	x	x
Bloods**		x			x			x
Immunosuppressive Medications		x			x			x
Concomitant Medications		x			x			x
SRH (Child and Caregiver)		x	x	x	x	x	x	x
Educational Background		x						
School Absenteeism		x	x	x	x	x	x	x
HUI Questionnaire*		x	x	x	x	x	x	x
Caregiver Satisfaction Questionnaire (Caregiver)		x	x	x	x	x	x	x
Patient Navigator Satisfaction Questionnaire (Caregiver)						x	x	x
Events of interest			x	x	x	x	x	x
Hospitalisation			x	x	x	x	x	x
Data linkage (NDI, ANZDATA, MBS, PBS)								x
Qualitative interviews/questionnaires (subset of participants only)					x[#]			x
PedsQL[***]		x	x	x	x	x	x	x

mo = months

*HUI only to be completed by participants aged 3 years and above.

** Physical examination and blood test are not mandatory

[#] Waitlist group visit 4 interview can be done any time from post-randomisation to before the start of intervention

***PedsQL completed only by some participants**. PedsQL for children 1 month and above.

7. STUDY POPULATION

7.1 RECRUITMENT PROCEDURE

Participants will be recruited from sites across Australia. There will be two channels for recruitment. Firstly, the sites' principal investigator, or delegate, will identify potentially eligible participants from the existing KCAD cohort study. Secondly, potentially eligible patients will be identified from the respective hospital databases. To ensure voluntary consent, the site Principal Investigator will delegate responsibility for the informed consent discussion to appropriately trained study staff. As outlined in the patient information sheet and consent form (PISCF), all patients will be informed that their participation in the study is completely voluntary and their decision whether to participate will not impact their treatment or their relationship with treating clinicians in any way. For those who are involved in the existing KCAD cohort study, research staff will also emphasise that their participation in this study is separate to the other study and they are not obliged to participate.

7.2 INCLUSION CRITERIA

Specifically, to be eligible for the study, participants must satisfy all of the below criteria:

1. Children with CKD (1-5), or CKD-D or CKD-T.
2. Aged 0 -16 years (inclusive).
3. Low SES background and/or living in "rural/remote areas" (RA2-RA5). Low SES families are defined as one of the following (self-reported):

a. Weekly household income (less than the median gross household income, $1250 (AUD) per week),

b. Just getting along, poor or very poor self-perceived financial status,

c. Single parenting on social benefits,

d. Both parents are unemployed,

e. Families living in public housing.

4. Caregiver(s) speak English or caregiver(s) speaks a little English but has a family member who can speak English
5. Able to provide consent by the caregiver (and assent– if the child is 16 years of age).
6. Only one sibling from a family can be included in the study

7.3 EXCLUSION CRITERIA

1. Limited life expectancy of less than 12 months.

7.4 CONSENT

A written informed consent will obtained for the study. During COVID-19 pandemic at times where written informed consent cannot be obtained, a verbal consent will be obtained.

For children under 16 years, a parent or caregiver will give written or verbal consent on behalf of the child. Children under 16 who are considered by the investigator to be of requisite maturity to understand the study requirements will countersign the parent consent form or child will provide verbal consent along with parent verbal consent. For children aged 16 years a parent or caregiver will sign the parent consent form and the child will countersign the parent consent form or child will provide verbal consent along with parent verbal consent.

Participants who do not speak English and who also do not have caregivers/family members who speak English will be excluded from the study for feasibility reasons. Families with basic knowledge of English who can be assisted by English speaking children or other family members can be included in

the study. This level of communication will be sufficient for the navigator assisting participants with day-to-day navigation activities. These families will have access to a phone interpreter service during consent and study visits for data collection. The key study information sheet will be translated to some of the most commonly used language other than English.

Only one of the sibling/s from a family will be included in the study. The parent/caregiver will choose the child who will participate in the study.

All PISCFs will be approved by a responsible Human Research Ethics Committee (HREC) with jurisdiction for the participating site prior to the beginning of the trial at each site. Participating sites will send a copy of the PISCF to the coordinating centre (AKTN) for review prior to submitting it to their HREC/regulatory office. A copy of the final approved version will also be filed with the AKTN following approval from the site HREC/regulatory office. Standardised PISCFs have been formulated by the Trial Management Committee (TMC) and included in the list of Appendices.

The site investigator's delegate undertaking the consent process will describe the study and answer any questions. After discussing the trial, ample time will be given to the patient, accompanying person and/or legal representative to enquire about the trial and decide whether to participate. No person involved with the trial will coerce or unduly influence the decision to participate in the trial.

A copy of the signed PISCF will be supplied to the patient and responsible supporters (i.e. witness). The original consent forms will be filed in the Site Trial Master File, and a copy placed in the patient's hospital medical record as required.

Consent forms and patient information sheets will be revised should any relevant and important new information become available and resubmitted for HREC and site governance approval.

For patient navigators and healthcare professionals taking part in the qualitative interview sub-study from all the sites, the consent will be obtained by the qualitative study team.

8. PARTICIPANT SAFETY AND WITHDRAWAL

8.1 RISK MANAGEMENT AND SAFETY

If there are any participants, or caregivers, who express any concerns or anxiety in relation to the patient navigator or survey questions they are asked, then the research staff can refer them to the appropriate services.

8.2 SAFETY MONITORING COMMITTEE (SMC)

An independent SMC will safeguard the interests of study participants, families and the patient navigators. The committee will ensure that all safety concerns regarding the safety and well-being of the child are appropriately managed by the investigators. The committee's role is to provide independent and timely review of any safety issues that arise during and from the trial. The TSC will retain sole decision-making responsibility for modifications to the trial.

The SMC will be constituted by the AKTN and operate in accordance with the trial specific SMC Charter. Members will have no financial or scientific conflicts of interest with the NAVKIDS^2 study. The members of SMC will include individuals with expertise in paediatrics, clinical trials, and clinical research in nephrology.

8.3 Event Of Interest Reporting

It is anticipated that significant risk/ events of interest related to the intervention and the study are very unlikely. Events of interest (hazards, incidents and complaints) will be collected throughout the study (see Table 2 and Table 3). The events of interest deemed urgent will be reported to the Coordinating Principal Investigator and AKTN within 48 hours of site becoming aware of the event. If any events of interest do occur, they will be reported by the study investigators to the HREC as per HREC requirement. The anticipated adverse effect which may have a direct impact on the child and caregiver may include time burden (including repeated study visits), psychological/mental distress associated with trial participation.

Handling of Withdrawals

A procedure has been generated for participants who have consented to take part in the study and then subsequently withdrawn. This may occur due to the death of the child, caregivers' unwillingness to continue completing future research-related tasks, at the treating physician's discretion or a change of mind with regard to participation more generally.

If the patient navigator intervention is stopped permanently for any reason, the participant is to continue participating and data collection will continue until the final study follow-up time point. If a participant expresses a wish not to complete questionnaires, they should remain in the study and other trial-related data will be obtained from medical records review unless participant has explicitly stated they do not want any further information collected.

8.4 Replacements

We anticipate a low dropout rate and so we will not recruit replacements for dropout.

9. Statistical Methods

9.1 Sample Size Estimation & Justification

The sample size was calculated for the analysis of the 5-point Likert scale of the SRH (and caregiver-rated health for younger children) of the child using an ordinal logistic regression. A target of 150-168 patients will be required for the analysis. It is assumed that the dropout rate will be low and so the sample size has not been inflated for dropout.

Table 3: Assumed distribution of the SRH (5-point Likert scale) for the control group (based on the KCAD study), and the power to detect the odds ratio (OR) for the intervention (and the corresponding distribution of the outcome in the intervention arm). [The estimated change in the proportion of patients reporting good/very good and excellent health before and after the intervention is based on published estimates from a clinical trial of complex intervention][42].

OR	**Power**		Poor	Fair	**Good**	**Very good**	**Excellent**
		Intervention	4%	12%	50%	20%	14%
2.3	0.83	Control	9%	22%	51%	12%	7%

This sample size will allow us to detect an OR of 2.3, with approximately 80% power and a significance level of 0.05. Data from the KCAD study indicated the OR of children from the lowest SES quartile reporting poor and fair health (compared with good, very good and excellent health) was at least 2.0[2]. Therefore, an OR of 2.3 is a clinically significant change in SRH with the proposed intervention.

A convenience sampling strategy will be taken for the exploratory endpoints aiming to collect PedsQL for 30 children 2 years and older and 5 children 1 year and younger across all sites**.**

9.2 Statistical Analysis Methods

Data analyses: The primary analyses will be conducted as close as possible to the intention-to-treat ideal so that we may estimate the effect of the patient navigator as it would happen in real life (e.g., staff leaving, staff on holidays, families not engaging). Per protocol analyses may be conducted as secondary analyses. The main statistical analyses of primary and secondary outcomes comparing the treatment arms will include CKD stage (CKD (1-5), CKD-D, CKD-T) and study centre as fixed effects. Additionally, outcomes with repeated measures will include the time point (modelled as categorical) and the interaction between time point and treatment arm in the model. Additional modelling with ad hoc adjustments may be performed if baseline characteristics are not sufficiently balanced between treatment groups (supporting analyses).

The primary outcome analysis is targeted at estimating the difference in SRH of the child between participants randomised to the immediate treatment and waitlisted groups at 6 months post-randomisation. All measures of child SRH from baseline to 6 months post-randomisation will be analysed using a cumulative logit mixed effects model, which will include a random intercept for each participant. The primary result will be the treatment effect estimate at 6 months post-randomisation and the 95% CI obtained from the model.

SRH of the caregiver will be analysed using similar approaches to SRH of the child. Secondary endpoints that are continuous, repeated measures, such as utility-based quality of life (HUI), will be analysed using linear mixed models. Count data measured at a single time point, such as number of hospitalisations, will be analysed using Poisson regression (or negative binomial or zero-inflated Poisson regression as appropriate) to compare the treatment arms at 6 months post-randomisation. These models will be extended to generalised linear mixed models (GLMMs) for repeatedly measured count outcomes (e.g., number of missed school days). Binary outcomes, such as hospitalisation (none vs at least one) at 6 months post-randomisation, will be analysed using logistic regressions. Descriptive analyses will be performed for the following outcomes: Death (all-cause, CV, non-CV; expected to be low for this patient population); CKD-related outcomes (e.g., graft failure, rejection); Caregiver satisfaction questionnaire items at each time point.

A p-value of 0.05 will be used to indicate statistical significance. All analyses after 6 months post-randomisation will be considered exploratory analyses. Full details of the planned statistical analyses may be found in the pre-specified Statistical Analysis Plan (SAP).

Economic evaluation: An economic evaluation will be conducted to determine the costs and benefits of a patient navigator program for improving the overall health of children with CKD. Initially, a within-trial economic evaluation will be conducted, which will be extended to a modelled evaluation over a longer time horizon, using a patient-level simulation model. Data sources, including the utility-based quality of life estimates to generate quality adjusted life years (QALYs), all other primary and secondary outcomes such as the proportion of participants reported better overall health, and costs

generated from the trial, will be included in the model. We will take a healthcare funder perspective; therefore, costs will include all intervention costs, all health care resource use over the trial duration, including inpatient admissions, ED presentations (duration and the number of times) and outpatient resource use. The inpatient admission and ED presentation information will be collected from parents and hospital medical records. Both costs and benefits will be discounted at 5% per year. An incremental cost per additional patient avoiding fair/poor health, and incremental cost per QALY gained in the intervention group, compared to the waitlisted group will be calculated with results plotted on a cost-effectiveness plane. Bootstrapping will be used to estimate a distribution around costs and health outcomes, and to calculate the confidence intervals around the incremental cost-effectiveness ratios. We will also use a patient level microsimulation model to examine costs and outcomes over a longer time horizon. A cost-effectiveness acceptability curve will be plotted to provide information about the probability that the intervention is cost-effective, given willingness to pay for each additional health outcome achieved. Any analyses using health utilities will be restricted to participants aged 3 years and above, and a sensitivity analysis will be conducted excluding children aged 3-4 years (as the HUI has not been validated for these ages). The economic evaluation will be undertaken by Wong, Howell and Howard.

Process evaluation: We will use a mixed methods approach to assess the barriers and enablers of acceptance and uptake of the program. All participating caregivers will complete the Patient Navigator Satisfaction Questionnaire at three time points (1 month into treatment, 3 months into treatment and immediately post-treatment), to assess their perception of the intervention over time. In addition, qualitative semi-structured interviews and questionnaires will be conducted by trained research personnel (with supervision from Investigators Tong and Howell) with a purposive sample of children and family members (min. n=20). There will be 2 interviews for all the participants in the interview sub-study - prior to the intervention and immediately post-treatment. The topics will include: acceptance of the patient navigator program, sufficient time spent by the patient navigator for individual patients, perceived barriers, challenges and enablers for implementing and the perceived benefits and harms of the intervention. Key questions will also be used to assess intervention fidelity regarding perceived care received by the participants. Assessment of intervention fidelity across the sites will also be carried out through key-informant interviews of study staff (n=20 interviews with patient navigators and healthcare professionals) assessing potential impact of this on the outcome. Questioning will also assess barriers and enablers to program sustainability (short and long-term) and implementation of the intervention into standard care. All patient navigators will complete attendance logs, to assess patient navigator time requirement. There will also be an interview conducted 1-month into treatment with approximately 5 patients from the immediate start group to determine if sufficient time has been allocated to navigator.

Exploratory Endpoints: Data collected for the PedsQL exploratory endpoints will be separately evaluated by the TORCH program team. The analyses will include head to head comparison of HUI3 and PedsQL, and evaluation of the relationships between SRH and PedsQL for children 3 years and older and the PedsQL infant scale for children 1 year and younger. These analyses will be undertaken by NAVKIDS Investigators, Howard, Howell and Wong (who are also TORCH investigators).

The analyses of the progression of kidney dysfunction and biomarkers will be exploratory and involve comparisons of the treatment arms using data collected at baseline, 6 months, and 12 months post-randomisation.

10. STORAGE OF BLOOD AND TISSUE SAMPLES

10.1 DETAILS OF WHERE SAMPLES WILL BE STORED, AND THE TYPE OF CONSENT FOR FUTURE USE OF SAMPLES

Blood samples will be collected as part of normal clinical practice and results recorded in the trial database. Samples collected outside usual clinic visits (refer section 6.3) will only be used for the purposes of this study. The study samples and any paperwork accompanying the samples collected outside usual clinic visits will be labelled with a study code only (without patients' names, addresses or hospital number). Blood samples will be destroyed in accordance with the laboratory protocol for that site, or pathology clinic.

11. DATA SECURITY & HANDLING

11.1 DETAILS OF WHERE RECORDS WILL BE KEPT & HOW LONG WILL THEY BE STORED

Electronic data will be captured and stored in REDCap, a central web-based database that is secure and password protected. Original consent forms, paper copies of questionnaires and case report forms will be stored in a locked cabinet accessible only to the researchers at the site where the participant was recruited (Centre for Kidney Research at the Children's Hospital Westmead, Sydney Children's Hospital Randwick, Queensland Children's Hospital Brisbane, Royal Children's Hospital Melbourne, Perth Children's Hospital,). This locally stored data will be in identifiable form as it will contain names, dates of birth and other identifiers. After closure of the trial, investigators will retain all study documentation, including consent documents, ethics committee approvals, and correspondence for a minimum of 15 years or according to local policy, or until the youngest child turns 25, whichever is the longest.

11.2 CONFIDENTIALITY AND SECURITY

Participants' records and the data generated by the study will be confidential. Any information that may identify a participant will be excluded from data presented in the public arena. Data will be stored in a secure, lockable location, and access to electronic data will be protected through a password protected web interface. The data extracted will be de-identified and a unique study number used. Similarly, data collected on the electronic case report form will be de-identified and a unique subject number will be used.

11.3 DATA SHARING

Data sets will be made available by the Central Coordinating Group to researchers within the NAVKIDS^2 Study collaborative for analysis of sub-studies and state specific outcomes after the primary manuscript has been accepted for publication.

For researchers outside the collaborative, individual participant data will be made available upon request to a Data Access Committee, a review board set up to assess proposals based on sound science, benefit-risk balancing and research team expertise. Appropriate data will be made available to approved proposals. This process will be in effect for a period of 2 to 5 years following publication of the main study results. After 5 years, the data will be available in the Sponsor's data warehouse but without investigator support other than deposited metadata.

12. QUALITY ASSURANCE

12.1 TRAINING AND EXPERIENCE

Each participating Principal Investigator will ensure site study staff have access to a computer with internet at their workstation to allow data entry into REDCap. All data collectors will receive an induction to using REDCap, and an operational user manual for REDCap will be provided to each unit. Site Principal Investigators and their co-investigators will also meet the following criteria.

- Commitment of sufficient time to conduct the study.
- Provide evidence of adequate training and experience to conduct the study.
- A willingness to recruit the requisite number of participants from their site.
- Provide evidence of proficiency in the tenets of Good Clinical Practice.

12.2 DATA MONITORING FOR GCP COMPLIANCE

Utilising a risk-based monitoring approach, a detailed monitoring plan will outline trial monitoring activities. Monitoring efficiency will be optimised by a system of remote monitoring performed by the Central Coordinating Group. If indicated, and with advance notice, study sites may be visited by a Clinical Monitor. The visits will be an opportunity to provide additional support and training to site staff, ensure the study is conducted according to the protocol, and in line with local regulatory requirements. Source documents from which the data are obtained will be made available during the visit to the Clinical Monitor for review.

13. APPENDICES

List of Attachments included:

Document Name	Version Number	Date
Caregiver questionnaire	1.1	22/05/2020
Patient navigator satisfaction questionnaire	1.1	22/05/2020
HUI - 3	2.1	22/05/2020
PedsQL	AKTN 1.0	13/03/2021
Patient navigator risk management plan	1	13/11/2018
Parent information sheet, consent and withdrawal form	6	31/03/2021
Young person information sheet	3	06/09/2019
Adult information sheet, consent and withdrawal form	3	28/09/2020
Medicare Information Sheet and Consent Form	2	22/06/2021
Navigator information sheet, consent and withdrawal form	3	28/09/2020
Health professional information sheet, consent and withdrawal form	3	28/09/2020

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