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# Outcome Measures of Clinical Trials in Pediatric Chronic Kidney Disease

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**Abstract:** Clinical trials of chronic kidney disease (CKD) in children have important implications for the early identification and management of CKD. The selection of clinical trial outcomes is critical for assessing the effectiveness of interventions in pediatric CKD clinical trials. This review systematically examines the spectrum of outcome measures deployed in pediatric CKD clinical trials, which includes clinical and alternative outcomes, patient-reported outcome measures (PROMs), and safety indicators. Alternative outcome measures were stratified into four levels of evidence strength: convincing, probable, suggestive, and inconclusive. Consequently, the selection of outcome measures for pediatric CKD clinical trials mandates careful consideration of both their methodological feasibility and the robustness of their evidence base. Moreover, the burgeoning field of PROMs warrants integration into the design of future pediatric clinical trials to enrich the relevance and impact of research findings.

**Keywords:** children; chronic kidney disease; clinical trial; outcome measure



**Citation:** Liang, Z.; He, G.; Tao, L.; Zhong, X.; Lin, T.; Jiang, X.; Ding, J. Outcome Measures of Clinical Trials in Pediatric Chronic Kidney Disease. *Future* **2024**, *2*, 56–66. https://doi.org/10.3390/future2020005

Academic Editor: Lloyd J. Kolbe

Received: 13 December 2023
Revised: 26 April 2024
Accepted: 30 April 2024
Published: 6 May 2024



## 1. Introduction

Chronic kidney disease (CKD), which had a global prevalence of 9.1% and affects 697.5 million people, was responsible for 1.2 million deaths in 2017 [1]. It ranked as the 18th leading cause of global disability-adjusted life-years (DALYs) lost, witnessing a 93% increase from 1990 to 2019 [2]. It is expected to become the fifth leading cause of death by 2040 globally [3]. Addressing CKD actively could contribute to achieving the United Nations' (UN's) Sustainable Development Goals (SDGs), specifically the goal of reducing premature mortality from non-communicable diseases by one-third by 2030 [4]. Children and adolescents with CKD and kidney failure face a higher risk of mortality that is estimated at 30 to 1000 fold of their healthy counterparts [5]. Moreover, they are at higher risk for end-stage kidney disease (ESKD) as well as cardiovascular diseases in adulthood [6]. The early identification and management of pediatric CKD have gained broad attention in recent years [7]. As a result, an increasing number of clinical trials on patients with pediatric CKD are being conducted.

The concept of clinical trials was initially introduced into the medical field, notably documented in the New England Journal of Medicine in 1952 [8]. It underwent gradual refinement and updates as the medical era progressed. Clinical trials are research studies that test a medical, surgical, or behavioral intervention in people [9,10]. Such interventions

can include drugs, cell and biological products, surgical procedures, equipment, behavioral therapies, and preventive care, with volunteers of all ages, including children. The choice of outcome measures in clinical trials is critical to assess whether the intervention is effective since different outcome measures lead to different conclusions.

In support of the continued development and assessment of clinical trials for pediatric CKD, this research retrieves information and articles related to clinical trials involving patients with pediatric CKD, sourced from both domestic and international registers. Subsequently, a comprehensive review of outcome indicators is conducted.

Clinical outcome measures used to scale trial outcomes can vary in classification methods. For instance, according to the study aims, outcomes can be divided into safety indicators, efficacy indicators, economic benefit indicators, and life quality indicators. According to response to the outcome, they can be classified into clinical outcome measures and surrogate outcome measures [11,12]. In addition, there are patient-reported outcome measures that have received increasing attention in recent years [13].

## 2. Clinical Outcome Measures

In line with the definition proposed by the Food and Drug Administration (FDA) in the US [14], indicators of clinical outcome refer to the indicator that directly measures whether the participants' sense and function are better or whether they live longer in clinical trials. By weighing clinical outcome measures such as the improvement in a certain symptom, clinical researchers value the benefit of the intervention, potential benefit, or whether the benefit outweighs the negative response, such as hepatic injury caused by a drug. For example, survival and kidney replacement therapy (KRT) are commonly used as clinical outcome measures in CKD patients. In pediatric CKD clinical research, the most commonly used outcome indicator is CKD progression but the definition of progress varies in different research.

### *2.1. Survival*

Survival is considered a paramount outcome in clinical trials, holding significant value for caregivers and children affected by CKD [15]. Despite its importance, survival outcomes are reported in a mere 14% of trials, a phenomenon attributed to the relatively low mortality rates observed within the short follow-up durations typical of clinical studies [16]. This gap underscores the challenge of capturing long-term outcomes and highlights the need for extended follow-up periods and larger cohort studies to adequately assess survival benefits in the CKD population.

### *2.2. KRT*

The definition of the outcome as the initiation of KRT or the preparatory phase for KRT is well-established [15]. As patients with CKD experience deterioration of kidney function to a certain extent, KRT becomes necessary to sustain life. The point at which KRT is initiated or is being prepared marks a stage of irreversible kidney decline and the need for life-sustaining treatment, which is perceptible to the patient. Therefore, the progression to KRT has the attributes necessary to serve as a clinical outcome indicator.

However, defining progress solely by the initiation of KRT presents several limitations as an outcome indicator in clinical trials. Firstly, due to the strong compensatory abilities of children's kidneys, CKD often progresses slowly. Relying on KRT as the sole outcome measure may lead to extended follow-up periods, a reduction in measurable outcomes, and increased sample size demands, thereby complicating the execution of clinical trials. Secondly, the criteria for initiating KRT vary globally, influenced by regional practices and external factors such as health insurance coverage [1]. This variability introduces heterogeneity when KRT initiation is used as an outcome measure in CKD clinical trials, particularly those spanning multiple regions. Such heterogeneity necessitates careful interpretation of study reports to account for these differences.

### *2.3. GFR and KRT as Composite Clinical Outcome Indicators for CKD Progression*

Given the critical nature of KRT, it serves as an outcome indicator while also integrating additional measures to create a composite clinical outcome indicator. Alternatively, KRT can serve as the primary outcome, with other indicators acting as secondary outcomes [15].

These supplementary indicators often encompass the glomerular filtration rate (GFR), estimated glomerular filtration rate (eGFR), or serum creatinine. While the majority of registered clinical trials do not specify the eGFR calculation formula used, GFR is a reflection of kidney function and its correlation with prognosis has been substantiated by numerous studies [17,18].

Contrary to earlier beliefs that GFR declines linearly once CKD is diagnosed, further research indicates that the progression may not be uniformly linear [19].

Currently, there is variation in defining progression through GFR metrics. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines describe progression as either (1) a decline in kidney function observed in a follow-up patient or (2) the onset of kidney failure, with the latter defined by the need for KRT to manage symptoms of renal function decline or complications [20]. While this definition is clear, its application in clinical trials can be complex [21,22]. As a result, some clinical trials adopt alternative definitions, such as a GFR decrease by 50% or 25% or a doubling of serum creatinine levels [23–25]. Moreover, some experts suggest that the rate of GFR decline should be considered in addition to the extent of the decline. Consequently, certain studies have utilized the rate of change per year or the eGFR slope [22]. The National Institute for Health and Care Excellence (NICE) in the UK recommends performing at least three GFR tests within a 90-day period and defines progression as an eGFR decrease of >5 mL/min/1.73 $m^2$ within one year or >10 mL/min/1.73 $m^2$ within five years [26]. Furthermore, the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines propose defining progression as an eGFR decrease of no less than 25% [17].

## 3. Alternative Outcome Measures

Certain clinical trials use alternative outcome measures instead of clinical outcome measures when clinical outcome indicators like death or KRT may not be available due to limited follow-up duration. Furthermore, given that the benefits of improving traditional outcome indicators are well-established, alternative indicators, such as blood pressure and urinary protein level, are widely used as surrogate outcomes [15].

The use of alternative outcome indicators as substitutes for clinical outcomes must be approached with great caution. A substantial body of epidemiological studies and clinical trials is necessary to validate the reliability of alternative outcome indicators for predicting the relationship between clinical interventions and patient benefits. Those alternative measures that have undergone extensive testing and are acknowledged by the FDA are often referred to as validated alternative outcome measures [27].

Alternative outcome indicators like biochemical data or imaging data are often used in clinical research because they require fewer samples, shorter follow-up times, and fewer resources to evaluate the effects of interventions. Nonetheless, these alternative indicators may not always accurately reflect clinical outcomes [28]. Many alternative outcome indicators have not been thoroughly validated, exhibit significant variability between individuals, and may not be relevant to patients. Relying on these unverified indicators can lead to clinical trial conclusions that do not address the needs of patients and clinicians and may lead to unnecessary testing of different alternative indicators. This not only wastes research resources but also limits the applicability of the findings to clinical decision making [29–33].

### *3.1. Clinical Test/Measurement Value as Surrogate Outcome Indicators*

Pediatric CKD typically progresses at a slow rate. In clinical trials, the limited follow-up duration and budget may not allow for the observation of a sufficient number of clinical outcomes, such as the initiation of KRT. Consequently, researchers may opt for surrogate

indicators that are closely associated with clinical outcomes. A surrogate endpoint is a measure used to predict the effect of an intervention on a primary outcome in a way that is in a shorter time, with less cost, or less invasive, allowing for early and valid conclusions about the intervention's impact on the actual primary outcome [34]. These indicators should theoretically be strongly correlated with the progression or prognosis of CKD and be supported by substantial evidence [29]. However, some indicators are still under investigation and evaluation.

Surrogate outcome indicators should adhere to the standards for risk factor–outcome association evidence established by the World Cancer Research Fund and the Global Burden of Disease, Injury, and Risk Factors Study 2019 [35]. We suggest that evidence criteria for these surrogate outcome indicators be categorized into four levels: convincing, probable, suggestive, and inconclusive (Table 1).

**Table 1.** Risk-outcome paired evidence definition.

| Level | Definition (Need to Meet All Requirements) |
| --- | --- |
| Convincing | Be confirmed by more than one research type<br>At least 2 independent cohort should be included among these research types<br>No apparent unexplained heterogeneity between the studies<br>Research is of high quality and thus is safe to conclude that the relation is not caused by random or systematic error including mix, measure error, and selection bias<br>Have a biologically plausible dose–response relationship<br>For the risk-outcome pairs, significant associations were required after considering the source of potential bias |
| Probable | Evidence from at least two independent cohort studies or at least five case-control studies<br>No apparent unexplained heterogeneity between the studies<br>This research is of high quality and thus is safe to conclude from that the relation is not caused by random or systematic error including mix, measure error and, selection bias<br>Have evidence of a biological plausibility |
| Suggestive | Have evidence from at least two independent cohort studies or at least five case-control studies<br>Although there may be some unexplained heterogeneity, the direction of the effects is generally consistent<br>Have evidence of a biological plausibility |
| Inconclusive | Allow any risk exposure with sufficient data to consider but insufficient evidence to exist for more definitive grading |

As depicted in Table 2, our review lists eight surrogate outcome indicators and their evidence levels in pediatric clinical trials.

**Table 2.** Surrogate outcome indicators and their evidence levels in pediatric CKD trials.

| Surrogate Outcome Indicators | Level |
| --- | --- |
| Proteinuria [36–47] | Convincing |
| Blood Pressure [41,48–50] | Convincing |
| Anemia [51] | Inconclusive |
| Hypoproteinemia [43,49,51] | Inconclusive |
| Dyslipidemia [43,52] | Inconclusive |
| Hyperphosphatemia [53] | Inconclusive |
| Hypocalcemia [54] | Inconclusive |
| Hyperuricemia [55] | Inconclusive |

#### 3.1.1. Proteinuria

Recognized in the KDIGO guidelines as a critical factor, proteinuria is also an essential marker in assessing the risk level of CKD [36]. Various methods are employed to quantify

proteinuria, including 24-h urinary protein quantification, the urinary protein–creatinine ratio, and the urinary albumin–creatinine ratio [21]. Extensive research has validated proteinuria as a risk factor for CKD progression in both glomerular and non-glomerular diseases [37–40]. Furthermore, the efficacy of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) in reducing proteinuria and slowing CKD progression has been well-established [41] (Table 2).

#### 3.1.2. Blood Pressure

High blood pressure is a significant independent risk factor for the progression of CKD in children [39,48–50]. Approximately 50% of children with CKD exhibit high blood pressure, with masked hypertension (random surges of dynamic blood pressure) being more common [48,56]. It has been observed that nearly 36% of children undergoing antihypertensive treatment still experience occasional systolic or diastolic blood pressure readings above the 90th percentile for their age and sex, indicating uncontrolled hypertension [48]. The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial showed that, over five years, maintaining blood pressure below the 50th percentile for the age and sex of the child could delay CKD progression [41]. This finding suggests that strict blood pressure control could be an effective target for reducing the risk of CKD progression. However, a comparison of blood pressure control between 2005–2008 and 2010–2013 from the Chronic Kidney Disease in Children study (CKiD) revealed no significant improvements in hypertension management over time among 851 participants [57]. This indicates that despite long-standing recognition of hypertension as a risk factor, screening and treatment for high blood pressure in children with CKD remain suboptimal. Enhanced blood pressure control is necessary to decelerate the progression of CKD in this population (Table 2).

#### 3.1.3. Inconclusive Indicators

Under the risk factor–outcome paired evidence criteria, several clinical tests or measurement indicators have yet to meet the 'highly likely' or 'probable' evidence thresholds. While associations with CKD progression have been observed in cohort or case-control studies for indicators such as hypoproteinemia, dyslipidemia, anemia, hyperphosphatemia, hypocalcemia, and hyperuricemia, there is insufficient evidence to definitively endorse them as surrogate outcome indicators of CKD progression. These indicators currently fall under the 'no conclusion' category, necessitating additional research to ascertain their evidential strength. Subsequent research has shown a link between hypoalbuminemia and CKD progression, independent of proteinuria levels, in both glomerular and non-glomerular diseases [43,49,51]. These findings suggest that monitoring and addressing low blood albumin levels in children with CKD could hold clinical value in slowing disease progression (Table 2).

Anemia was an outcome measure used commonly. It is typically defined by hemoglobin levels falling below the fifth percentile for the standard values of the same age and sex, potentially due to albumin loss from proteinuria. While anemia has been associated with CKD progression, especially in non-glomerular diseases, the underlying mechanisms are not fully understood [51]. It may serve as an indicator of tissue hypoxia, which could lead to renal damage. Hypoxia may stimulate the production of the extracellular matrix and the release of profibrotic cytokines in renal tubular cells, thereby hastening kidney disease progression [58]. Additionally, anemia could exacerbate the decline in renal function by diminishing oxygen delivery, prompting ischemic changes, and causing endothelial damage (Table 2).

Dyslipidemia was an outcome measure commonly used in clinical trials, with the majority of interventions involving pharmaceuticals. In these studies, dyslipidemia was identified as a risk factor for cardiovascular disease, which is a leading cause of death in CKD patients. In children with CKD, dyslipidemia showed a significant correlation with the disease's progression [43,52]. Unlike in adults with CKD, where multiple confounders

contribute to dyslipidemia, the primary confounder in children is obesity. Even after adjusting for body mass index (BMI), the relationship between dyslipidemia and CKD progression remains significant [43,52]. The association may be due to factors such as insulin resistance and elevated apolipoprotein C-III levels [59–61], as well as decreased lipoprotein lipase activity in target tissues and altered lipoprotein receptor levels [62]. Further research is required to confirm these potential mechanisms (Table 2).

Uric acid was used as an alternative outcome indicator in some clinical trials. Research on the link between high uric acid levels and CKD progression in children is limited. It has been observed that compared to children with uric acid levels below 5.5 mg/dL, those with uric acid levels of 5.5–7.5 or >7.5 mg/dL experienced a 17% or 38% faster progression to advanced stages of CKD [55]. The relationship between uric acid levels and the progression of CKD, as well as the potential role of uric acid-lowering medications in delaying this progression, requires further exploration (Table 2).

## 4. Patient-Reported Outcome Measures (PROMs)

PROMs are based on standardized and validated questionnaires completed by patients to evaluate their perspectives on their own functional status and well-being [63,64]. These measures emphasize the importance of individual perspectives in assessment and have been widely implemented in clinical trials, medical decision making, healthcare quality management, policy reform, and other areas [63]. Maximizing patient quality of life and capturing the whole child and family in healthcare decisions was ranked as one of the most important themes in both the Standardized Outcomes in Nephrology—Children and Adolescents (SONG-Kids) initiative [15] and KDIGO Controversies Conference [65].

PROMs used in pediatric CKD trials primarily included questionnaires assessing the preference for disposable growth hormone syringes based on pain and convenience, the Medical Outcomes Study Questionnaire Short Form 36 (SF-36) to evaluate patient quality of life (with the study ongoing), subjective evaluations of hospitals performing related kidney transplants (completed but unpublished), the Kidney Disease Quality of Life Short Form (KDQOL-SF) for assessing CKD patient quality of life (published but without KDQOL-SF results), and End-Stage Renal Disease Adherence Questionnaire (ESRD-AQ) alongside self-designed scales to assess the impact of a mobile online tool for disease detection (completed but unpublished) [66–68]. These studies primarily gather patients' subjective experiences of their disease and recovery and apply them as outcome indicators in clinical research, though results are seldom published.

The burden of CKD on patients and their families is profound, contributing to high rates of mortality and morbidity and adversely affecting the quality of life of patients and caregivers [69]. They face a complex therapeutic regimen, which may include polypharmacy, dietary restrictions, fluid intake limitations, regular medical appointments, and the challenges associated with KRT. Children with CKD often exert additional effort to maintain developmental milestones and growth compared to their healthy peers [15,70]. They also face a higher risk of educational deficits, cognitive disorders, and poorer occupational, psychological, social, and behavioral outcomes than healthy children, with these consequences extending into adulthood [71–73]. Important aspects of living with CKD, such as anxiety, school attendance and performance, social participation, hospitalization rates, and fatigue, are critical for children yet are not commonly measured or reported in trials [29]. Therefore, future research development may benefit from a greater focus on clinical trials that address patient needs.

## 5. Safety Indicators

Adverse event reporting, including death, readmission in hospital, acute kidney injury, and contrast-induced nephropathy are commonly included as safety indicators in pediatric CKD trials [74]. These indicators mainly reflect clinical outcomes.

## 6. Gaps and Perspective

At present, clinical trials focused on pediatric CKD often fail to report outcomes crucial to patients and their caregivers, affecting the evidence's applicability and trustworthiness for decision making [65]. This lack of comprehensive reporting restricts the practical use of trial findings in clinical settings and policy development. Managing CKD in children is complex due to the variety of immediate and future impacts of treatments and the different priorities of patients, their families, and medical professionals. The effectiveness of decision making in pediatric CKD care is hindered by the lack of consistent reporting on outcomes crucial to patients and caregivers. Specifically, essential outcomes like mortality and infection rates are seldom disclosed, with only 14% and 29% of trials reporting these outcomes, respectively [16,29]. This inconsistency limits the comprehensive understanding necessary for informed healthcare decisions. There are several gaps existing in the outcome of clinical trials in CKD children currently. Firstly, survival and KRT are pivotal outcomes in clinical trials for CKD in children, yet their rare occurrence and slow progression pose challenges for research. The necessity for surrogate outcome indicators has led to the exploration of biomarkers as potential outcome measures. However, currently, most of these newly developed biomarkers lack sufficient evidence for risk factor–outcome association with clinical outcome measurements such as survival and KRT. Key areas of uncertainty include developing platforms for biomarker studies, assessing the validity of biomarkers in predicting disease progression and treatment response, and integrating biomarkers, imaging, and biopsies into a cohesive clinical management strategy for CKD [65]. Despite the growing acknowledgment of the significance of PROMs in recent years, their inclusion in pediatric CKD trials remains limited. A systematic review found that only 10% of the different outcome domains reported were PROMs and these were often excluded from the majority of studies [29]. This underscores the necessity to discern which PROMs tools are most suitable for regular CKD management and which are best employed under specific conditions, aiming to enhance patient-centered care in pediatric nephrology research and practice.

## 7. Conclusions

Evaluating outcome indicators in clinical trials is crucial for advancing research focused on children with CKD. In pediatric trials, clinical outcome indicators are of paramount interest to both patients and researchers. However, relying solely on clinical outcomes can complicate trial execution. Alternative outcome indicators are frequently utilized, with some, like proteinuria and blood pressure, already established as relevant to CKD progression. Nonetheless, the efficacy of many alternative indicators in representing true clinical outcomes is yet to be determined. Furthermore, the significance of these alternative measures to patients and their families warrants additional investigation. Future studies might benefit from prioritizing patient-centered outcomes and incorporating validated health-related quality-of-life instruments tailored for children with CKD. This approach could enhance the utility of clinical trial findings, providing richer insights for patients and healthcare practitioners to better manage and improve patient outcomes.

**Author Contributions:** Conceptualization, Z.L., G.H., X.J. and J.D.; methodology, L.T., T.L. and X.Z.; Literature search and sorting, Z.L. and G.H.; data curation, Z.L., G.H., T.L. and L.T.; writing—original draft preparation, Z.L. and G.H.; writing—review and editing, all authors; supervision, X.J. and J.D.; funding acquisition, X.Z., T.L. and X.J. All authors have read and agreed to the published version of the manuscript.

**Funding:** This work was funded by The National Key Research and Development Program of China (2022YFC2705100, 2022YFC2705101 to X.J., 2022YFC2705104 to X.Z.), the Beijing Natural Science Foundation (Z190023 to X.Z.), and the Joint Funds of the National Natural Science Foundation of China (U21A20383 to T.L.).

**Institutional Review Board Statement:** Ethical review and approval were waived for this study focusing on clinical outcome settings that do not involve individual humans or animals.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** The data presented in this study are available in this article.

**Acknowledgments:** We thank Yangfeng Wu of Peking University Clinical Research Institute for his helpful guidance in the conceptualization of the manuscript.

**Conflicts of Interest:** The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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