

End Point Selection in ADPKD Clinical Trials



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Autosomal dominant polycystic kidney disease (ADPKD) is the leading hereditary cause of kidney failure. Challenges have arisen in developing consensus-based clinical trial end points endorsed by the wider ADPKD research community and regulators. Disease progression in ADPKD occurs slowly and is highly variable between patients. Clinical end points such as death or kidney failure occur infrequently and late in the condition. Thus, their use as outcomes in ADPKD trials requires prolonged follow-up and large sample sizes. Furthermore, because of the nature of ADPKD progression, surrogate outcomes such as change in glomerular filtration rate (GFR) or kidney volume, have varying validity in different populations of patients with ADPKD. Alternative trial approaches, such as enriching trial populations with patients at high risk of disease progression, have the potential to mitigate some of these challenges, although they limit the generalizability of results. The emergence of novel trial designs presents potential approaches to alleviate some of these issues. This paper explores some of the unique features of ADPKD from which difficulties in outcome selection arise, examines how modern trial designs can lessen some of these features, and provides an overview of commonly reported outcomes in ADPKD trials.

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ADPKD is characterized by the progressive growth of fluid-filled kidney cysts, accompanied by expansion of kidney volume and decline in kidney function.¹ A single disease-modifying therapy has been developed for the condition—the vasopressin V2 receptor antagonist, tolvaptan.² However, the prescription of tolvaptan is limited to patients with rapidly progressing disease, has a potentially serious side effect profile, and is of high cost. Thus, a need remains for accessible efficacious therapies that can slow the progression of the condition. Complexities exist in establishing consensus-based clinical trial end points that are accepted and employed by the ADPKD research community and therapeutic regulators

globally. Progression of ADPKD occurs slowly, and accepted clinical end points for assessing chronic kidney disease (CKD) progression, such as a halving of the estimated GFR (eGFR) or culmination to kidney failure, are late occurring and infrequent events. To assess these as primary outcomes, clinical trials would require extended follow-up periods and large sample sizes to demonstrate significance.³

Trials in ADPKD tend to use surrogate outcomes, such as change in eGFR or total kidney volume (TKV). However, the abilities of these surrogate measures to predict long-term clinical outcomes vary in the diverse population of patients with ADPKD. Furthermore, though kidney function and kidney and cyst volumes are the most reported surrogate outcomes, they are far from the only outcomes used. Nearly 100 different outcome domains have been identified across ADPKD trials.⁴ This diversity in outcomes limits pooling data from trials in meta-analyses, thereby reducing evidence certainty.⁵

Emerging innovative trial designs such as platform trials have the potential to facilitate enrollment of

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larger populations observed over extended follow-up durations, over which slow occurring outcomes (such as mortality) may be observed.

This article explores the unique features of ADPKD from which difficulties in outcome selection arise and how different trial designs can mitigate some of these features. It also provides an overview of common outcomes in ADPKD trials.

ADPKD Overview

Disease Progression

Symptoms of ADPKD commonly present in early adulthood. Detectable cyst growth for a diagnosis of ADPKD, when there is a positive family history, is as follows: ≥ 3 cysts (unilateral or bilateral) in individuals aged 15 to 39 years, ≥ 2 cysts in each kidney when aged 40 to 59 years, and ≥ 4 cysts in each kidney for individuals aged ≥ 60 years.⁶ During early stages of the condition, cyst growth causes irreversible damage to kidney structures and leads to expansion of TKV. Despite this, kidney function is maintained because compensatory hyperfiltration of the surviving nephrons preserves eGFR. Eventually, the persistent growth of cysts causes kidney damage exceeding this hyperfiltration capacity, resulting in loss of kidney function.^{7,8} Symptoms of ADPKD include pain and hematuria; and comorbidities include hypertension, chronic urinary tract infection, cardiac disease, and intracranial aneurysms, all of which impact quality of life (QoL).^{7,9}

Disease Variability

ADPKD progression is highly variable, due in part to genetic variability in the condition. Pathogenic variants in *PKD1* or *PKD2* have been reported to account for approximately 80% and 15% of cases of typical ADPKD phenotypes, respectively. Clinical cohorts of people with kidney cysts vary¹⁰ and the identification of rarer genetic etiologies, such as *GANAB*, *ALG5*, *ALG9*, *DNAJB11*, *NEK8*, and *IFT140*, indicate the broader genomic complexity.^{11–15} The average age at which patients progress to kidney failure highlights the spectrum of disease progression.¹⁶ For patients with truncating pathogenic variant ADPKD-*PKD1*, the median age of kidney failure was 55 years; in those with nontruncating variant, this was delayed to 67 years; and in individuals with ADPKD-*PKD2*, kidney failure did not develop until the age of 79 years.¹⁷

Furthermore, even within families who presumably have the same genetic variant, intrafamilial variability has been observed.^{18,19} Additional factors influencing disease progression include polygenic contributions and environmental exposures.²⁰ Understanding the risk of progression for each individual patient is

important for judicious prescription of appropriate therapeutic interventions to those who will obtain benefits, while minimizing potential harms in those unlikely to experience a clinically meaningful effect.

Risk Stratification

Given the variability of ADPKD progression, risk stratification tools have been developed to assess individual risk of disease progression. The Mayo Imaging Classification system characterizes patients as having typical or atypical ADPKD based on cyst distribution; then uses height-adjusted TKV and age to categorize patients into groups, namely low risk (1A), intermediate risk (1B), or high risk (1C–E) of decline in kidney function, and onset of kidney failure. Patients in category 1E are predicted to have an estimated frequency of kidney failure at 10 years of 66.9%, compared with just 2.4% in category 1A.²¹ The Predicting Renal Outcome in Polycystic Kidney Disease (PRO-PKD) scoring system considers factors, including the genetic variant present, sex (defined as a set of biological attributes that are associated with physical and physiological features), and age at symptom onset, to allocate patients into 3 categories, namely low, intermediate, or high risk of progressing to kidney failure.¹⁷

ADPKD Trial Populations

The design of ADPKD trials needs to consider the unique features of the condition and the heterogeneity in presentations and severity of the condition. One option to address the slow progression of ADPKD when designing trials has been to enrich the population with individuals deemed at higher risk of rapid progression. This may be based on progression risk scores or on enrolling patients with evidence of reduced kidney function. A Mayo Imaging Classification score of 1C to 1E or a Predicting Renal Outcome in PKD score > 6 may indicate a person at higher risk of progression.^{17,21} *Post hoc* analyses of the TEMPO3:4 trial of tolvaptan applied the Predicting Renal Outcome in PKD (PROPKD) score system to patients and found that tolvaptan significantly slowed eGFR decline in the intermediate and high risk groups; however, there was no difference in the low-risk group.²² It is worth considering that patients in Mayo Imaging Classification class 1C are particularly heterogeneous.

Nevertheless, because kidney function decline is preceded by irreversible cyst-induced structural damage, interventions employed once evidence of kidney function loss is apparent may be deployed too late in the condition. This limits the applicability of trial results of efficacious therapies to those in earlier disease stages for whom long-term benefits might be compounded.

An additional consideration when determining ADPKD trial populations is the concurrent use of medications, particularly tolvaptan. Tolvaptan is indicated for patients with rapidly progressing disease, who may be ideal trial candidates as outlined above. Tolvaptan has an acute effect on kidney function, potentially confounding kidney function–related outcomes. One potential approach to address this is to permit the recruitment of patients on tolvaptan who have already been stabilized on therapy. However, though it is possible to encourage establishment of therapy before commencement, beneficial therapies should not be withheld if they become suitable during the follow-up period.

Established challenges in recruiting to clinical trials apply to ADPKD trials and pragmatic decisions about inclusion criteria may be required. It is unlikely to be necessary to avoid recruiting from families, given the intrafamilial variability present in ADPKD.^{18,19} Although genetic testing is becoming increasingly available, this will often not be a pragmatic option for the purposes of clinical trial recruitment, and should not be a barrier to recruitment for trials; however, when available, it may permit further analyses. Furthermore, the development of PKD trials which use gene and mRNA therapies will require a confirmed genetic diagnosis to facilitate enrollment, further adding to the value of a genetically confirmed PKD diagnosis.

ADPKD Trial Design

Emerging options for improving the efficiency of clinical trials are the use of adaptive trial designs and registry-based randomized controlled trials.²³ These novel designs are pragmatic in nature and may facilitate the enrollment of larger numbers of participants for a longer follow-up period at more modest costs than traditional designs.²³

Adaptive trial designs allow for modifications to the trial protocol based on the results of interim analyses, in accordance with prespecified rules. Multiple trial arms are dynamically evaluated, allowing several interventions to be assessed simultaneously, with arms added or dropped throughout the trial. STAGED-PKD was a 2-stage adaptive study which randomized patients with ADPKD to venglustat 8 mg or 15 mg once daily or placebo in the first stage, followed by placebo or venglustat in stage 2, with the dosage depending on the results of stage 1.²⁴

Platform trials focus on a disease state rather than an intervention.²⁵ Platform trials may not have a pre-determined end date and run for extended periods, such that longer-term outcomes (such as kidney failure or death) may be able to be observed.²⁵ The CKD

Adaptive Platform Trial Investigating Various Agents for Therapeutic Effect is an adaptive platform trial in which interventions and participants will be added as the trial grows.²⁶

Registry-based randomized controlled trials use the large stores of data in electronic medical records and registries to support lower cost research.²⁷ Randomized trials may be conducted by controlling exposure allocation and the registry data are reviewed for results. One of the benefits of these trials is their ability to facilitate enrollment of more diverse populations than traditional randomized controlled trials. In conditions where patient prognosis is highly variable, such as ADPKD, this evaluation of large and diverse populations is desirable. However, issues may arise with consistency in the quality of data collected. Ideally, countries should have well-established national registries in place for the collection of robust trial data.²⁸ Interventional registry-based studies primarily focus on well-defined clinical end points, such as mortality.²⁸ In [Figure 1](#), we show key considerations in trial design for ADPKD patient cohorts.

ADPKD Outcomes

Outcomes for clinical trials should be relevant to patients and clinicians, likely to manifest over the course of a trial and be measured in an accurate, reproducible, and financially feasible way. Outcomes may be considered in 3 categories:^{3,29}

- Clinical end points: an event or comorbidity which can be objectively diagnosed by a clinician.
- Surrogate end points: intermediate outcomes (such as imaging or other biomarkers) which act as substitutes for clinical outcomes.
- Patient-reported outcomes: health outcomes which are reported by patients and are directly relevant to how they function or feel.

In addition, outcomes should be recognized by regulatory bodies for the approval of new therapies. Although some outcomes may be highlight-valuable to consumers (e.g., cardiovascular disease [CVD]) they may not meet requirements for regulatory approval. Most notably, the first landmark trial of tolvaptan used change in TKV as the primary outcome²; the use of this surrogate outcome was cited as one of the reasons that regulatory approval was initially denied in the United States.

Recent years have seen the conclusion of many interventional ADPKD trials, in which outcomes have been heterogeneously reported. The variability of outcomes in ADPKD trials has been explored previously.⁴ Across 68 trials published between 2001 and 2019, there were 97 reported outcome

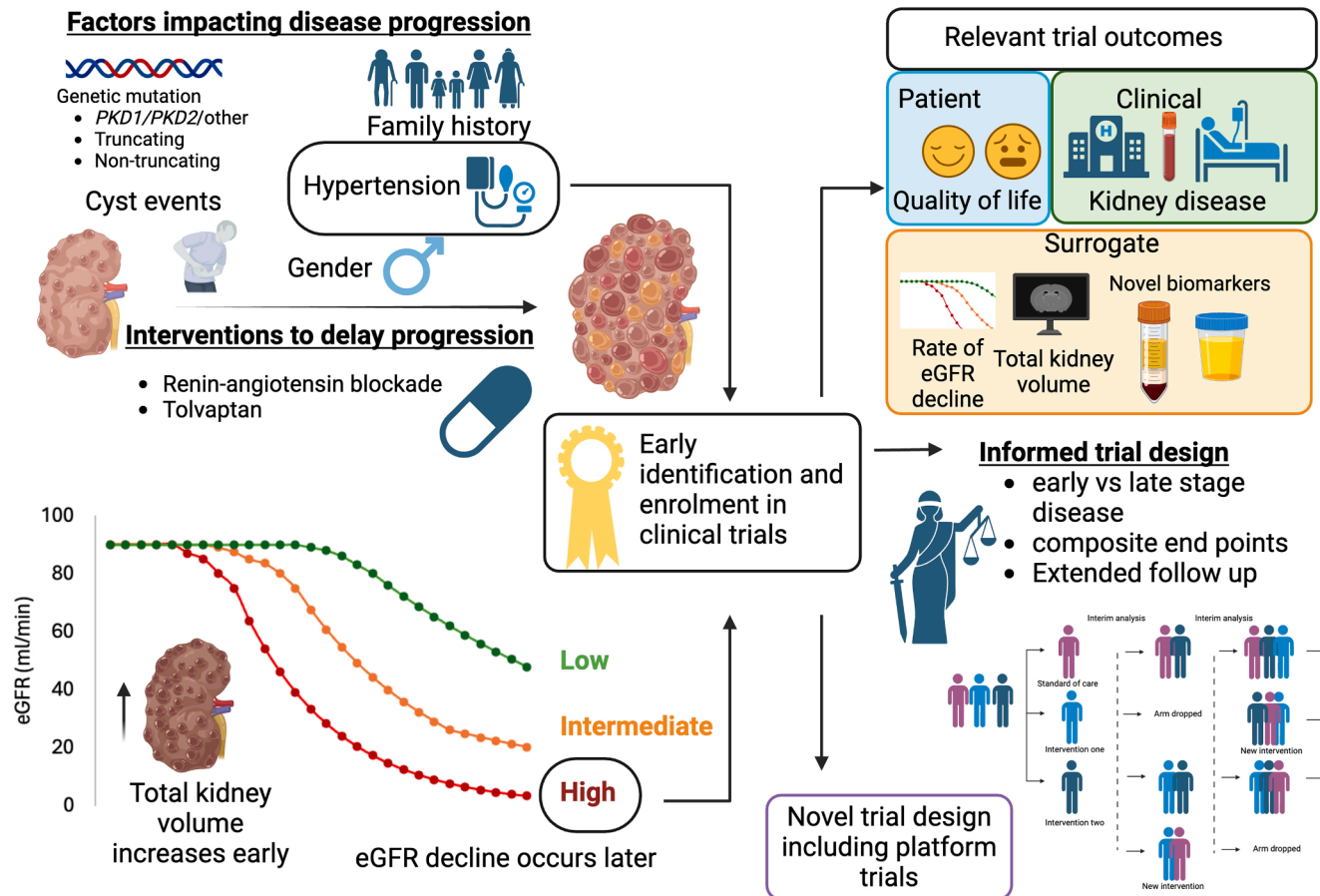


Figure 1. Key considerations in trial designs for ADPKD patient cohorts. Trial designs require consideration of clinical factors which drive disease progression, including genetic mutations, family history, hypertension, gender, and use of disease-modifying therapy on progression. Ideally, trials would target those at high risk of disease progression and consider an array of clinical outcomes, including patient-reported outcomes, clinical outcomes, and surrogate outcomes. Innovative trial design may improve research in ADPKD. ADPKD, autosomal dominant polycystic kidney disease; eGFR, estimated glomerular filtration rate. Created in BioRender. BioRender.com/n18p333.

domains; outcomes were surrogate in 42% of studies, clinical in 31%, and patient-reported in 27%. Only 2 outcomes were reported in > 50% of trials: kidney function and kidney or cyst volume. In contrast, > 90 different outcome domains were reported in < 20% of trials.⁴

In Table 1,^{2,24,30-38} we summarize key interventional trials in ADPKD, including their primary outcomes. The heterogeneity of outcomes across ADPKD trials makes evaluating the relative efficacy of therapies more difficult, prevents aggregation of data in meta-analyses, and increases risk of outcome reporting bias.⁵

The Standardised Outcomes in Nephrology—Polycystic Kidney Disease (SONG-PKD) project evaluated outcome measures based on the priorities of patients with PKD, their family members, clinicians, researchers, and policy makers.^{39,40} They aimed to determine a core outcome set which should be used in trials to report relevant findings.³⁹ They identified 4 “core” outcome domains which are as follows: kidney function, mortality, cyst pain, and CVD. Outcomes,

such as cyst growth and blood pressure were among the 11 “middle tier” outcomes, which were defined as critically important to some stakeholder groups. An additional 23 outcomes were listed in the “outer tier” and were important to some stakeholder groups.³⁹ A summary of commonly reported outcomes in ADPKD trials and their SONG-PKD ranking is provided in Table 2. The following discussion provides an overview of outcomes, which have been implemented most frequently in ADPKD trials⁴ or are of high patient priority.⁴¹ In Figure 2, we summarize these outcomes.

Kidney Function

By definition, a decline in kidney function is fundamental to the development of kidney failure. Kidney function has been identified as a core outcome in the SONG-PKD initiative, in part because of its value as a signal for kidney failure.^{39,40} Kidney function may be reported in trials using various measures, most commonly, change in eGFR, measured GFR, serum creatinine, or creatinine clearance.⁴ Although a

Table 1. Summary of the design and outcomes of key trials in ADPKD

Trial	Trial details	Primary outcome and main findings
Kidney function outcomes		
Torres <i>et al.</i> ³⁰ (REPRISE)	Population: 1370 patients with ADPKD, aged 18–55 yrs with eGFR of 25–65 ml/min per 1.73 m ² or aged 56–65 yrs with eGFR of 25–44 ml/min per 1.73 m ² . Intervention: tolvaptan, morning and afternoon at 60 mg and 30 mg, respectively, up to 90 mg and 30 mg vs. placebo.	Primary outcome: change in eGFR. Main findings: tolvaptan participants had eGFR decreased by 2.34 ml/min per 1.73 m ² , compared with 3.61 ml/min per 1.73 m ² in the placebo group.
Meijer <i>et al.</i> ³¹ (DIPAK 1)	Population: 309 patients with ADPKD, aged 18–60 yrs and eGFR of 30–60 ml/min per 1.73 m ² Intervention: lanreotide 120 mg SC once every 4 wks in addition to standard care vs. standard care only for 2.5 yrs	Primary outcome: annual change in eGFR assessed as slope through eGFR values during treatment phase Main finding: annual rate of eGFR decline in lanreotide-treated participants was −3.53 ml/min per 1.73 m ² /yr, compared with −3.46 ml/min per 1.73 m ² /yr in the control group
Kidney volume outcomes		
Schrier <i>et al.</i> ³² (HALT-PKD, Study A)	Population: 558 patients with ADPKD, aged 15–49 yrs, eGFR > 60 ml/min per 1.73 m ² , elevated BP Intervention: 4 arms in a 2-by-2 design combination lisinopril and telmisartan vs. lisinopril and placebo, at 2 levels of BP control	Primary outcome: % change in TKV over time Main findings: participants in the low BP group had a 14.2% slower annual increase in TKV compared with those in the standard BP group.
Torres <i>et al.</i> ² (TEMPO3:4)	Population: 1445 patients with ADPKD, aged 18–50 yrs, with a TKV > 750 ml, and eCrCL > 60 ml/min Intervention: tolvaptan, morning and afternoon at 45 mg and 15 mg, respectively, increased to 90 mg and 30 mg vs. placebo	Primary outcome: annual rate of change in TKV. Main findings: tolvaptan participants had a TKV increase of 2.8%/yr and eGFR decreased 2.72 ml/min per 1.73 m ² /yr vs. placebo patients. TKV increases 5.5%/yr and eGFR, decrease −3.81 ml/min per 1.73 m ² /yr in the placebo group
Walz <i>et al.</i> ³³	Population: 433 patients with ADPKD, eGFR of 30–89 ml/min per 1.73 m ² (or eGFR ≥ 90 ml/min per 1.73 m ² if single kidney volume exceeded 1000 ml) Intervention: everolimus 2.5 mg twice/d or placebo	Primary outcome: change in TKV Main finding: in year 1, TKV increased by 102 ml in the everolimus group, and by 157 ml in the placebo group (<i>P</i> = 0.02) in year 2, TKV increased by 230 ml in the everolimus group and 301 ml in the placebo group (<i>P</i> = 0.06). eGFR decreased 8.9 ml/min per 1.73 m ² in the everolimus group and 7.7 ml/min per 1.73 m ² in the placebo group (<i>P</i> = 0.15)
Mixed outcomes		
STAGED-PKD, Gansevoort <i>et al.</i> ²⁴	Population: 236 (stage 1) and 242 (stages 2) patients with ADPKD, MIC class 1C, 1D, or 1E, eGFR of 30–89.9 ml/min per 1.73 m ² Intervention: Stage 1: venglustat 8 mg vs. venglustat 15 mg vs. placebo. Stage 2: venglustat 15 mg vs. placebo	Primary outcome: rate of change in TKV over 18 mo in stage 1 and eGFR slope over 24 mo in stage 2 Main findings: prespecified interim futility analysis showed treatment had no effect on the annualized rate of change in TKV over 18 mo (stage 1) and had a faster rate of decline in eGFR slope over 24 mo (stage 2). Owing to this lack of efficacy, the study was terminated early
Perico <i>et al.</i> ³⁴ (ALADIN 2)	Population: 100 adults with ADPKD and eGFR 15–40 ml/min per 1.73 m ² Intervention 2 IM injections of 20 mg octreotide-LAR or 0.9% sodium chloride solution (placebo) every 28 d for 3 yrs	Primary outcome: coprimary outcomes, 1-yr TKV growth and 3-yr GFR decline Main findings: compared with placebo, octreotide-LAR reduced median (95% CI) TKV growth from baseline by 96.8 (10.8–182.7) ml at 1 year (<i>P</i> = 0.027) and 422.6 (150.3–695.0) ml at 3 yrs (<i>P</i> = 0.002). Reduction in the median (95% CI) rate of GFR decline (0.56 [−0.63 to 1.75] ml/min per 1.73 m ² /yr) was not significant (<i>P</i> = 0.295)
Torres <i>et al.</i> ³⁵ (HALT-PKD, Study B)	Population: 486 patients with ADPKD, aged 18–64 yrs, eGFR of 25–60 ml/min per 1.73 m ² , elevated BP Intervention: lisinopril and telmisartan vs. lisinopril and placebo	Primary outcome: time to death, kidney failure ^a or a 50% reduction from the baseline eGFR Main findings: no significant difference in the composite primary outcome was detected between the 2 treatment groups
Other outcomes		
Mekahli <i>et al.</i> ³⁶	Population: 91 patients with ADPKD, children aged 4–17 yrs, body weight ≥ 20 kg, eGFR ≥ 60 ml/min per 1.73 m ² Intervention: tolvaptan, morning and afternoon at 15 mg and 7.5 mg, respectively, up to 60 mg and 30 mg according to body weight and tolerability vs. placebo	Primary outcome: spot urine osmolality and spot urine specific gravity (coprimary end points) at 1 wk Main findings: least squares mean reduction in spot urine osmolality at week 1 was greater with tolvaptan (−390 mOsm/kg) than placebo (−90 mOsm/kg; <i>P</i> < 0.001), as was specific gravity (−0.009 vs. −0.002; <i>P</i> < 0.001)
Brosnahan <i>et al.</i> ³⁷	Population: 51 patients with ADPKD, without diabetes, eGFR 50–80 ml/min per 1.73 m ² Intervention: metformin up to dose 2000 mg/d vs. placebo	Primary outcome: coprimary end points of percentage of participants prescribed the full, or at least 50% of the randomized dose Main findings: 50% of metformin treated participants tolerated the full prescribed dose, compared with 100% in the placebo group
TAME PKD, Perrone <i>et al.</i> ³⁸	Population: 97 patients with ADPKD eGFR > 50 ml/min per 1.73 m ² Intervention: metformin up to 100 mg twice daily vs. placebo.	Primary outcome: safety and tolerability Main findings: 28 metformin-treated participants reduced drug dose because of intolerance, compared with 14 in the placebo arm.

ACEi, angiotensin converting enzyme inhibitor; ADPKD, autosomal dominant polycystic kidney disease; ARB, angiotensin receptor blocker; BP, blood pressure; CI, confidence interval; eCrCL, estimated creatinine clearance; eGFR, estimated glomerular filtration rate; HALT-PKD, The Halt Progression of Polycystic Kidney Disease trial; IM, intramuscular; MIC, Mayo Imaging Classification; REPRISE, Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD; SC, subcutaneous; TEMPO3:4, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV, total kidney volume.

^aInitiation of dialysis or preemptive transplantation.

Table 2. Summary of pros and cons of key outcome measures in ADPKD trials

Outcome domain	Outcome measures	Pros	Cons	Pragmatism	SONG priority
Kidney function	Estimate GFR, measured GFR, serum creatinine	Reflective of disease progression to kidney failure	Preserved in early disease. Measured GFR is most accurate but least accessible	Serum creatinine and GFR estimations routinely conducted	Core outcome
Kidney imaging	Total kidney volume, total cyst volume, parenchymal volume	Reflective of disease progression in early disease	Conflicting evidence on overall utility for long-term disease progression	Varying tests of differing accuracy and accessibility available	Middle tier
Urinary biomarkers	Proteinuria, albuminuria most common	Already consistently reported in trials, low cost and noninvasive assessment	Less clinical relevance to clinicians and patients	Easily obtained from patients in clinic	Outer tier
Cyst pain	Kidney, abdominal, epigastric	Directly influences patient quality of life and is of high priority for patients	Not necessarily reflective of disease progression	Easily reported by patients using questionnaire	Core outcome
Cardiovascular disease	Myocardial infarction, arrhythmias, fibrillation	Highly relevant to patients and clinicians, large morbidity and mortality burden	Inconsistently reported in trials	Clinical outcome to be observed	Core outcome
Blood pressure	Diastolic BP, systolic BP, mean arterial pressure	Measures are easily obtainable, low cost, and noninvasive	Not necessarily reflective of disease progression	Easily measured either in clinic or at home	Middle tier
Mortality	All-cause or cause specific mortality	Relevant clinical outcome	Infrequent and late occurring, would require large trial sample size	Clinical outcome to be observed	Core outcome

ADPKD, autosomal dominant polycystic kidney disease; BP, blood pressure; GFR, glomerular filtration rate; SONG, standardised outcomes in nephrology study.

measured GFR provides an accurate measure of kidney function, it is costly, time consuming, and less widely available than methods of estimation. An eGFR is

usually obtained from serum creatinine and calculated with formulae, such as the CKD-Epidemiology Collaboration equation.⁴¹

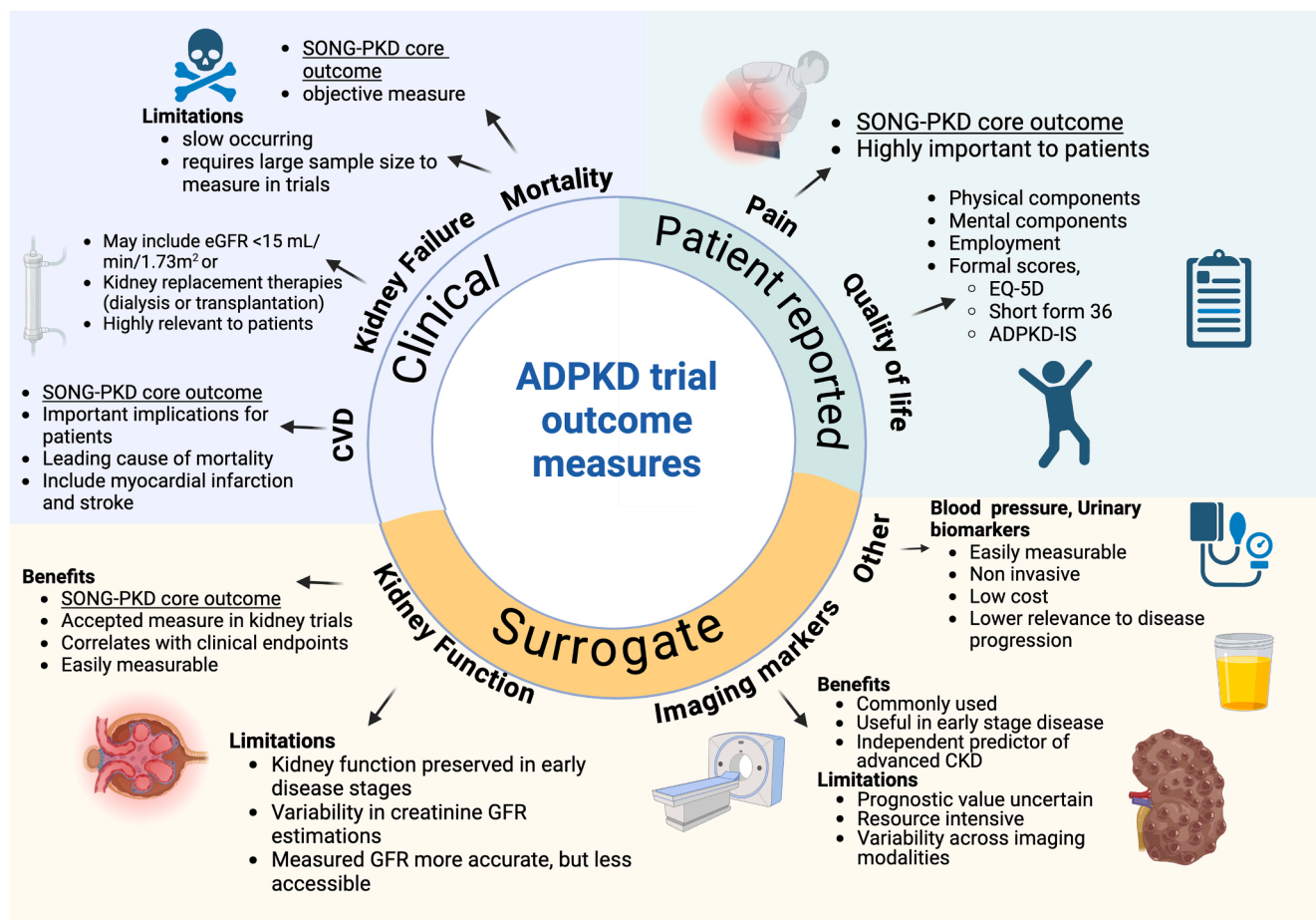


Figure 2. Summary of ADPKD trial outcome measures. ADPKD outcomes may be considered as clinical, surrogate, or patient reported. Outcome selection for trials should consider the relevance of the outcome to patients and clinicians, the likeliness of the outcome to manifest over a feasible trial duration, and the ease of measurement. ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated GFR; GFR, glomerular filtration rate. SONG-PKD, the Standardised Outcomes in Nephrology—Polycystic Kidney Disease study. Created in BioRender. BioRender.com/x72k677.

Different eGFR-based end points may be used in clinical trials to analyze observed kidney function, both inside and out of a trial paradigm. Total slope reports the overall change in eGFR over follow-up period; when the decline is linear over the follow-up period, a linear single-slope model may characterize trajectory.⁴² Those in high-risk groups (e.g., Mayo Imaging Classification class 1D or 1E) tend to have more linear decline in kidney function from an earlier age than those with lower progression risk.¹ In addition, some therapies exert acute effects on eGFR (e.g., tolvaptan), such that a linear model is not suitable. Instead, the chronic slope may be measured following initiation of an intervention, minimizing any acute effects an intervention may exert on eGFR.⁴² Modeling different statistical analysis may be complex and should involve trial statisticians. Trials may consider clinical outcome measures, which are reflective of kidney function, such as commencement of kidney replacement therapy or a 30% reduction in eGFR; however, these often require longer follow-up periods.

The main limitation of change in kidney function as an outcome is the relative stability of GFR in early ADPKD. The heterogeneity in measures of kidney function adds further complexities when considering kidney function as a trial outcome.

Kidney function measures have been used in major ADPKD clinical trials (Table 1). Of particular note, change in eGFR was the primary outcome measure of the Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD trial, which enrolled participants in later stages of ADPKD.³⁰ Kidney function is also well-recognized by regulatory bodies as an outcome for clinical trials of kidney diseases.

The progressive change in kidney function in patients with ADPKD has been well-documented. *Post hoc* analysis of the Halt Progression of PKD (HALT-PKD) trials found that most participants with ADPKD demonstrated a linear progressive decline in eGFR. Participants in study B (baseline eGFR: 25–60 ml/min per 1.73 m²) were more likely to have progressive disease than those in study A (baseline eGFR > 60 ml/min per 1.73 m²) (81% and 62.5%, respectively), and less likely to have stable eGFR (6% vs. 15.6%, respectively).⁴³

Kidney and Cyst Volume

As discussed, cyst growth begins early in the natural progression of ADPKD, while eGFR is still preserved. In these instances, volume measures may provide more insight into the stage and probable progression of the condition. TKV is the most reported imaging measure

in ADPKD trials.⁴ Other image-based measures, such as total cyst volume, parenchyma volume, and total cyst number, are less commonly reported.⁴⁴

Using TKV as a trial outcome requires precise measurements to enable quantifying potentially small changes.⁴⁵ Kidney imaging may be obtained through the following:

- Ultrasound: It is noninvasive and readily available; however, accuracy in determining volume is limited and subject to interobserver variability. Ultrasound may lack precision necessary to measure small changes over the short term of a clinical trial.
- Computed tomography: It has greater resolution and the ability to detect small cysts.
- Magnetic resonance imaging: It is often the modality of choice, can be limited by cost and availability.

Volume is estimated from imaging results, using one of multiple methods that are available.⁴⁴ There is a trade-off between accuracy and the resources required to produce a volume measure. Increasing automation and artificial intelligence algorithms have the potential to decrease the resources required and increase the accuracy of TKV estimations.⁴⁶

TKV has been used as a primary outcome in key ADPKD trials (Table 1), such as HALT-PKD study A and the Tolvaptan Efficacy and Safety in Management of ADPKD and Its Outcomes (TEMPO 3:4) trial. Both trials enrolled participants with early stages of ADPKD with eGFR > 60 ml/min per 1.73 m² at baseline.^{2,32}

The longest, prospective, observational cohort study of patients with ADPKD documenting changes in TKV has been the Consortium for Radiologic Imaging Studies of PKD. Originally, 241 participants were enrolled and have been followed-up with after 3, 8, and 13 years.^{47–49} At 13 years, the odds ratios of reaching each CKD stage per 100 ml/m increment in height-adjusted TKV were 1.38 (95% confidence interval: 1.19–1.60) for stage 3, 1.42 (95% confidence interval: 1.23–1.64) for stage 4, and 1.35 (95% confidence interval: 1.18–1.55) for stage 5.⁴⁹ An observational study of 2355 patients aimed to assess the prognostic value of age, TKV, height-adjusted TKV, eGFR, sex, race, and genotype on the probability of a 30% decline in eGFR.⁵⁰ They found TKV to be the most important prognostic factor: for a 40-year-old subject with an eGFR of 70 ml/min per 1.73 m², the adjusted hazard ratios for a 30% decline in eGFR were 1.86 for a 2-fold larger TKV (600 ml vs. 1200 ml) and 2.68 for a 3-fold larger TKV (600 ml vs. 1800 ml).⁵⁰ It should be noted that, this study recognized that individuals with *PKD1* genotype had a shorter median time to progression of 30% decline of eGFR and had higher baseline TKV than those with ADPKD-*PKD1*.

However, > 40% of patients lacked genetic data and no distinctions was made between truncating and nontruncating *PKD1* variants. The OVERTURE study enrolled 3409 participants and found that each additional ml/m of height-adjusted TKV was associated with a lower eGFR and more rapid eGFR decline as well as a greater likelihood of hypertension, kidney pain, and hematuria.⁵¹

There is some debate over the prognostic value of TKV. Following TEMPO 3:4, an open label extension trial was undertaken, TEMPO 4:4.⁵² In this trial, 871 TEMPO 3:4 participants were prescribed tolvaptan therapy with a primary end point of change in TKV from TEMPO 3:4's baseline to TEMPO 4:4 month 24. Over this extended time frame, the between-group difference in TKV observed at the end of TEMPO 3:4 was not maintained. At the end of TEMPO 4:4, "early treated" tolvaptan patients had a cumulative TKV increase of 29.9% versus 31.6% in "delayed treated" participants ($P = 0.38$). In contrast, between group differences in eGFR were maintained at each time point throughout TEMPO 4:4.⁵² Furthermore, there have been multiple interventional trials, which demonstrated a benefit of TKV that has not reflected a benefit on kidney function⁵³; for example, in Walz *et al.*'s³³ study of everolimus for the management of ADPKD (Table 1). TKV increased by 230 ml over 24 months in the everolimus group compared with 301 ml in the placebo group ($P = 0.06$). However, there was not a concurrent preservation of eGFR (change in eGFR: -8.9 ml/min per 1.73 m² on everolimus vs. -7.7 ml/min per 1.73 m² on placebo, $P = 0.15$). From these data, Walz *et al.* concluded that TKV is not a suitable surrogate marker for kidney function or end point for assessing therapeutic interventions.³³ This conclusion has been questioned on the premise that most everolimus-treated participants were in the later stages of ADPKD with reduced eGFR, precluding improvement in kidney function and that longer follow-up would have been required to determine whether the change in TKV predicted a change in eGFR.⁵⁴

Patient-Reported QoL and Pain

The progression of ADPKD and the manifestation of comorbidities have the potential to drastically impact patients' QoL. Cyst pain was identified as a core outcome in the SONG-PKD initiative.³⁹ Across ADPKD studies, patients have demonstrated lower mental and physical QoL scores than the general population.⁵⁵ QoL also tends to decrease as the condition progresses; a European cross-sectional study evaluating QoL in patients with ADPKD across CKD stages showed that health-related QoL was highest in patients with CKD stages 1 to 3, followed by transplant recipients and

patients with CKD stages 4 to 5, whereas patients on dialysis reported the lowest scores.⁵⁶ In addition, lower levels of employment have been recorded in patients with ADPKD at later stages of CKD.⁵¹

There are various methods by which QoL may be measured, including then following:

- ADPKD Impact Scale: This was developed specifically for ADPKD. This scale consists of 14 items that measure 3 domains (physical, emotional, and fatigue) and 4 additional questions on guilt, sleep, size or shape of abdomen, and urinary frequency or urgency.⁵⁷
- EuroQol 5-dimensional questionnaire: This is a descriptive system of health-related QoL scores covering 5 dimensions of health, with 3⁵⁸ or 5 levels,⁵⁹ and a child-specific measure.⁶⁰
- Short Form 36 survey: It assesses 8 health concepts, and is designed for self-administration.⁶¹
- Kidney Disease QoL Instrument: It consists of the Short Form 36 survey combined with 43 kidney disease-specific questions.⁶²

Factors directly impacting QoL have been commonly identified as particularly important to patients with ADPKD and their caregivers, including cyst pain or bleeding, ability to work, mobility or physical function, financial impact, anxiety or stress, and fatigue.⁶³ A thematic review identified "unvalidated pain" as substantially contributing to the unpredictability of daily living and preventing patients from establishing long-term goals.⁶⁴ Although the importance of outcomes directly impacting QoL is clear, they are infrequently and inconsistently reported across ADPKD; less than a quarter of ADPKD trials have reported on pain.⁴

Urinary Biomarkers

In the setting of CKD, urinary biomarkers tend to increase in concentration as kidney function declines and may be reflective of function. Increasing concentration of protein in the urine is commonly used in CKD evaluation, and proteinuria may act as marker of ADPKD progression specifically. Proteinuria is negatively correlated with eGFR. In the Modified Diet in Renal Disease study, higher levels of proteinuria were associated with a steeper decline in eGFR in patients with ADPKD.^{65,66} Established proteinuria has been correlated with higher mean arterial pressures, larger kidney volumes, and lower creatinine clearances than nonproteinuric patients with ADPKD.⁶⁷ Increased levels of urinary albumin excretion may be valuable as a marker of severity because it presents before a decline in eGFR is evident.⁶⁸ Additional urinary biomarkers that have been identified as reflective of

ADPKD progression include β 2-microglobulin, monocyte chemotactic protein-1, and kidney injury molecule-1.^{66,69}

There are many potential benefits of using urinary biomarkers as clinical trial outcomes. Their collection is noninvasive and relatively inexpensive.⁷⁰ Albuminuria and proteinuria are already regularly measured in trials and practice.⁴ However, urinary biomarkers may not be as clinically relevant to stakeholders; proteinuria was identified as an outer tier outcome in ADPKD.³⁹

CVD and Hypertension

Patients with ADPKD have an increased risk of CVD, which is a leading cause of morbidity and mortality in this group. The most common forms of CVD in patients with ADPKD have been identified as ischemic heart disease, arrhythmias, and heart failure.⁷¹ Largely because of its significant potential impact on life, CVD was identified as a core outcome in SONG-PKD.³⁹ However, it is infrequently reported in trials and specific measures vary.⁴

Hypertension is a common comorbidity often manifesting before kidney function begins to decline.⁷² Hypertension has been associated with more rapid progression of ADPKD and is considered an independent risk factor for developing kidney failure.⁷³ Hypertension likely plays an important role in cardiovascular mortality of patients with ADPKD and is a SONG-PKD middle tier outcome.³⁹ Antihypertensive agents acting on the renin-angiotensin system have been shown to slow ADPKD progression. In the HALT-PKD study A, targeting a lower blood pressure (95/60 to 110/75 mm Hg vs. 120/70 to 130/80 mm Hg) resulted in a significantly lower annual percentage increase in TKV.³² Blood pressure is an easily accessible outcome that can be regularly measured by the clinician or patient. It is the third most frequently reported outcome in ADPKD trials.⁴

Future Directions

Future trials will need to continue considering the unique features of ADPKD progression in their design. This may result in trials separated with differential outcomes for early versus late disease, similar to what occurred with the tolvaptan,^{2,30} or employment of composite outcomes to increase statistical efficacy. The importance of outcomes to patients should be considered, particularly the impact of interventions on pain and QoL.

The potential role for novel trial designs in patients with ADPKD could facilitate the enrollment of larger and more diverse populations with longer follow-up. These trials may allow for multiple interventions and outcomes to be assessed, thereby increasing efficiency.

Furthermore, statistical power calculations and sample size estimation for future ADPKD trials are critically dependent on careful end point and outcome selection. Key factors in this space to be considered are trial cohort enrichment; disease and progression assumptions; trial time frame; estimated investigational product effect size; and the specific outcome measure (Table 2) including reliability, applicability, and variability. The variety of clinical trials in ADPKD to date across different outcome measures and investigational products (Table 1) provide substantial context and information to inform approaches to future power calculations and sample size estimation.

Conclusion

There is an ongoing need for therapies that slow the progression of ADPKD and alleviate the symptom burden for patients. Establishing consensus on appropriate clinical outcomes for ADPKD trials will help facilitate comparison of interventions across studies, strengthen the evidence base for emerging therapies, and define clinically meaningful treatment effects.

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