Trials

STUDY PROTOCOL

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Implementation of Metformin Therapy to Ease Decline of Kidney Function in Polycystic Kidney Disease (IMPEDE-PKD): study protocol for a phase III, multi-centre, randomized, placebo-controlled trial evaluating the long-term efficacy of metformin in slowing the rate of kidney function decline in patients with autosomal dominant polycystic kidney disease

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Abstract

Background Autosomal dominant polycystic kidney disease (ADPKD) is the fourth most common reason for commencement of dialysis globally. There is an urgent need for treatments to slow the loss of kidney function and prevent complications in people with ADPKD. A growing body of evidence suggests metformin may have a therapeutic role in slowing cyst progression in ADPKD.

Methods IMPEDE-PKD is a prospective, multicentre, international, double-blind, randomized controlled trial of metformin versus placebo in adults with ADPKD. From November 2022, a total of 1174 participants will be targeted for recruitment globally, from participating kidney units in Australia, the UK, New Zealand, India, Hong Kong, South-East Asia and Europe. Following a 10-week run-in phase of extended-release metformin up-titrated to a maximum dose of 2000 mg, participants will be randomized 1:1 to receive either metformin or placebo and followed for 2 years. The primary outcome will be the rate of kidney function decline measured as a change in the estimated glomerular

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filtration rate. Secondary outcomes include other clinical markers for ADPKD progression (albuminuria, development of kidney failure), mortality, health-related QOL, pain, medication side effects, tolerability and cost-effectiveness.

Discussion If proven effective, metformin would positively impact the well-being of people with ADPKD as a treatment option that is widely available and affordable.

Trial registration ClinicalTrials gov NCT04939935. Registered on 25 June 2021.

Keywords Autosomal dominant polycystic kidney disease, Metformin, Clinical trial

Administrative information

Title {1}	Implementation of Metformin Therapy to Ease Decline of Kidney Function in Polycystic Kidney Disease (IMPEDE-PKD): study protocol for a phase III, multi-centre, randomized, placebo-controlled trial evaluating the long-term efficacy of metformin in slowing the rate of kidney function decline in patients with autosomal dominant polycystic kidney disease
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Name and contact information for the trial sponsor {5b}	The University of Queensland (UQ) acting through the Australasian Kidney Trials Network (AKTN). The trial sponsor can be contacted at aktn@uq.edu.au or on + 61 7 3443 7881
Role of sponsor {5c}	The Australasian Kidney Trials Network will be the Central Coordinating Centre and will be responsible for convening and reporting to the Global Steering Committee (GSC). The GSC will be responsible for the oversight of the study. AKTN will also be responsible for developing and maintaining charters for the GSC and Data and Safety Monitoring Board (DSMB)

Introduction

Background and rationale {6a}

Autosomal dominant polycystic kidney disease (ADPKD) has an estimated prevalence of 1 in 1000 in the general population [1]. The condition is characterized by exponential cyst growth that damages and distorts normal kidney tissue, culminating in enlarged painful kidneys and progressive chronic kidney disease (CKD) [2]. The only disease-modifying therapy currently available for ADPKD is tolvaptan, a vasopressin receptor antagonist. However, its widespread use is limited by side effects, high cost and restricted availability [3]. New condition-specific therapies to slow the rate of cyst growth and the progression of kidney function decline are crucial for improving patient outcomes and reducing healthcare spending. Metformin is an oral glucose-lowering agent prescribed to 150 million people globally for Type 2 diabetes mellitus (T2DM) [4], with a growing body of preliminarily evidence suggesting it may be beneficial in patients with ADPKD [5].

Cyst growth is dependent on the proliferation of cyst-lining epithelial cells and the secretion of fluid into the cyst lumen [6]. Metformin activates AMP-activated protein kinase (AMPK), which inactivates the molecular target of rapamycin pathways, thereby inhibiting cell proliferation and impairing cyst growth and expansion [7, 8]. Additionally, the secretion of fluid into the cyst lumen is mediated through cystic fibrosis transmembrane conductance regulator (CFTR) channels in the membrane of

epithelial cells. AMPK negatively regulates CFTR channels, which in turn decreases fluid secretion. Thus, as an activator of AMPK, metformin has a potential therapeutic role in slowing cyst growth rate in ADPKD through these two mechanisms [9].

Given its extensive use in the T2DM population, metformin has a well-established safety and tolerability profile. It is associated with self-limiting gastrointestinal disturbances (diarrhoea, nausea and vomiting) in 20–30% of recipients [10]. These can be managed by utilizing extended release (XR) preparations of metformin and slow up-titration to target dose [10]. Vitamin B12 deficiency occurs in around 6% of patients due to reduced gastric absorption [11]. However, this can be supplemented. There is also infrequent association with lactic acidosis (< 10 per 100,000 patient-years) [12]. As metformin is primarily excreted unchanged through active tubular secretion in the kidneys, drug dosage needs to be reduced as kidney function declines.

Initial studies have evaluated the safety and tolerability of metformin in people with ADPKD [13–18]. The Trial of Administration of MEtformin to tame PKD (TAME-PKD) study (NCT02656017) was a phase II, double-blind, randomized placebo-controlled trial of immediate-release metformin up to 1000 mg twice daily [17]. Ninety-seven participants aged 18–60 years with an estimated glomerular filtration rate (eGFR) > 50 mL/min/1.73 m^2 were recruited and randomized 1:1 to either metformin or placebo. After 2 years of follow-up, 40 metformin and 42 placebo participants remained in the study. Two participants withdrew from the metformin group due to adverse events, and one from the placebo group. However, 43% of participants in the metformin arm reduced the dose due to inability to tolerate the full dose. Metformin was evaluated as safe and tolerable, and there was a numerically smaller decline in eGFR; however, this trial was underpowered to detect significance [17]. In a second double-blind, randomized feasibility study led by the University of Colorado (NCT02903511), 51 participants with ADPKD and an eGFR between 50 and 80 mL/min/1.73 m^2 were recruited and randomized to immediate-release metformin or placebo, up to 1000 mg twice daily [18]. Among the participants in the metformin group who completed the study, only 50% received the full prescribed dose because of intolerable gastrointestinal side effects, but 82% tolerated more than half of the prescribed dose (median dose of all participants was 1500 mg per day). Changes in height-adjusted total kidney volume (htTKV) and eGFR were not statistically significantly different between the groups, but the decline in eGFR was smaller in the metformin group despite participants in this group having more severe disease [18].

Current experimental evidence suggests that metformin may slow the rate of cyst growth and kidney function decline in ADPKD. Despite the scientific rationale for its potential therapeutic role in ADPKD, the question of its efficacy requires the conduct of an adequately powered randomized controlled trial. This publication provides details of the protocol for the Implementation of Metformin Therapy to Ease Decline of Kidney Function in Polycystic Kidney Disease (IMPEDE-PKD) trial, which is a global, double-blinded, randomized controlled trial of metformin XR compared with placebo for 2 years in people with ADPKD, aged between 18 and 70 years, with an eGFR between 38 and 90 ml/min/1.73 m^2, and risk factors for a decline in kidney function.

Objectives {7}

The primary objective of IMPEDE-PKD is to evaluate the long-term efficacy of metformin therapy in slowing the rate of kidney function decline in subjects with ADPKD, measured as the change in eGFR (using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation) compared to placebo at 2 years from randomization.

Trial design {8}

IMPEDE-PKD is a phase III, international, prospective, blinded, parallel-group, superiority, randomized controlled trial, in which 1174 adults will be targeted for randomization in a 1:1 ratio to metformin or placebo and followed up for 2 years. An outline of the trial design can be seen in Fig. 1.

Methods: participants, interventions and outcomes

Study setting {9}

A total of 1174 adults with ADPKD will be targeted for recruitment from participating kidney units in Australia, New Zealand, the UK, India, Europe, Hong Kong and South-East Asia.

Eligibility criteria {10}

Inclusion criteria: To be eligible to participate in this trial, participants must satisfy ALL of these inclusion criteria:

1. Able to provide informed consent
2. Aged 18–70 years
3. Diagnosis of ADPKD based on radiological ± genetic criteria as per the Kidney Health Australia Caring for Australians and New Zealanders with Kidney Impairment (KHA-CARI) Guidelines [19]

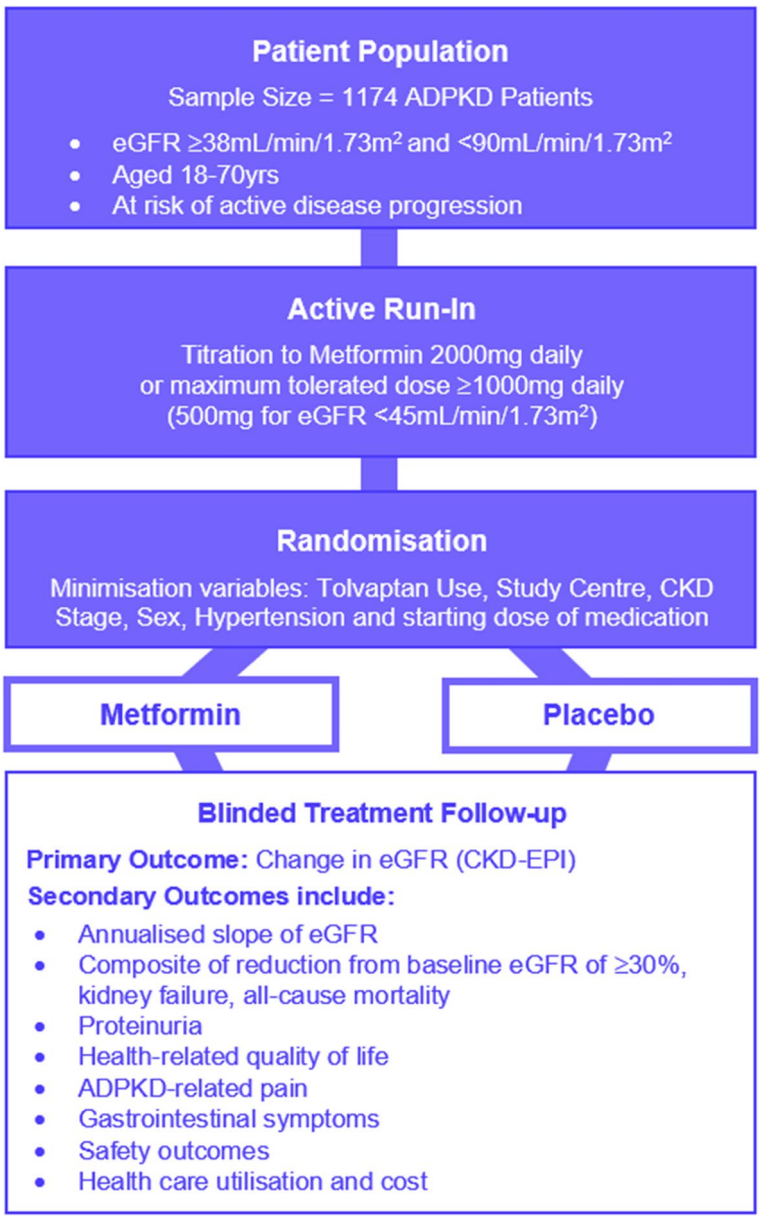

Fig. 1 IMPEDE-PKD study schema. ADPKD, autosomal dominant kidney disease; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate

4. eGFR ≥38 mL/min/1.73m^2 and <90 mL/min/1.73 m^2 (eGFR measured within the previous 6 months will be used for initial screening, and the current eGFR measured in the baseline blood test after receiving informed consent will determine eligibility to enrol)
5. Have either a or b:

a) One or more risk factors of ADPKD progression from the following:

- Bilateral kidney length ≥16.5 cm
- Total kidney volume (TKV) ≥750mL or htTKV ≥600 mL/m^2
- Mayo class IC/D/E or Pro-PKD score ≥6

OR

b) Evidence of active ADPKD progression defined by one of the following

- Decline in eGFR ≥ 5 mL/min/1.73m^2 in one year

- Decline in eGFR ≥ 3 mL/min/1.73m^2 per year over five years or more
- Increase in htTKV/TKV of≥ 5 % per year on at least 2 measurements in the past year, excluding any initial eGFR effect over the initial 3 months of tolvaptan commencement (if applicable)

6. For people on tolvaptan therapy, treatment must have been in place for at least six months with stable dosage for at least three months.

Exclusion criteria

Participants will be excluded if they have any of the following exclusion criteria:

1. Diabetes mellitus (as per American Diabetes Association definition), or other systemic conditions that may cause CKD independent of PKD (excluding hypertension)
2. Uncontrolled hypertension (systolic blood pressure >160 mmHg and/or diastolic blood pressure >100 mmHg after a period of rest)
3. Clinically significant heart failure, including but not limited to New York Heart Association Class III or IV
4. Any contraindication to metformin including abnormal liver function tests or untreated vitamin B12 deficiency
5. Currently taking metformin
6. Pregnancy or breastfeeding or planning to get pregnant in the next three years
7. Comorbidities with contraindication for metformin use or potential to contaminate trial outcomes, specifically active cancer, history of other solid organ transplantations, active chronic obstructive pulmonary disease, inflammatory bowel disease, and stoma
8. Non-polycystic liver disease, including but not limited to: a.) Liver enzymes (alanine transaminase, aspartate transaminase, or total bilirubin) >2 times the upper limit of normal, except when a diagnosis of Gilbert Syndrome exists and/or, b.) Child-Pugh classification score ≥5
9. History of dialysis

Who will take informed consent? {26a}

Participant consent forms will be approved by the Independent Ethics Committee (IEC) at each participating jurisdiction prior to the trial beginning at that jurisdiction. Trained research staff will introduce and discuss the trial in detail with participants, using the approved Participant Information Sheet and Consent Form (Supplementary 1). After discussing the trial, the participant, accompanying person, or legal representative will be given ample time to enquire about the trial and decide whether to participate before providing written informed consent. Participant consent must be obtained prior to the initiation of any trial procedures, including further screening to confirm eligibility from blood and urine tests. Participants will not start the run-in phase until a signed consent form is filed.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Participants in specific countries (Australia) will be asked to provide additional consent for the collection of buccal swab samples for potential further genetic testing and analysis. Participants can decline genetic testing on the consent form and still participate in the main trial.

Interventions

Explanation for the choice of comparators {6b}

Participants in the control group will receive matched identical placebo. A placebo-controlled trial was selected to rigorously evaluate the efficacy, safety and tolerability of metformin. The use of placebo as a comparator will increase the likelihood of detecting a treatment effect with a smaller sample size, thereby increasing research efficiency. The current justification for the use of a placebo comparator fulfils the criteria set out by the Declaration of Helsinki.

Intervention description {11a}

Because of the relatively high rate of gastrointestinal intolerance to immediate release metformin reported in pilot trials [17, 18] we chose treatment with a better tolerated extended release (XR) formulation of metformin [20].

At week 0 of the 12-week active run-in, all participants will start at the lowest dosage of metformin XR 500 mg tablets daily (taken with evening meal). This will be up-titrated every 4 weeks according to tolerability and kidney function. For participants with eGFR≥45 mL/min/1.73 m^2, the initial dose will be 2×500 mg up to a maximum of 2000 mg a day. Participants with eGFR values between38 and 44 mL/min/1.73 m^2 will start at 500 mg daily up to a maximum of 1000 mg per day. The metformin XR dose deemed to be tolerated by a participant during the week 10 phone visit will be the participant's starting dosage for the trial phase. An overview of dose titration during the run-in phase is provided in Fig. 2.

The metformin prescribed during the run-in phase will be stopped by all participants at week 10 followed by a 2-week wash-out period. At the conclusion of the

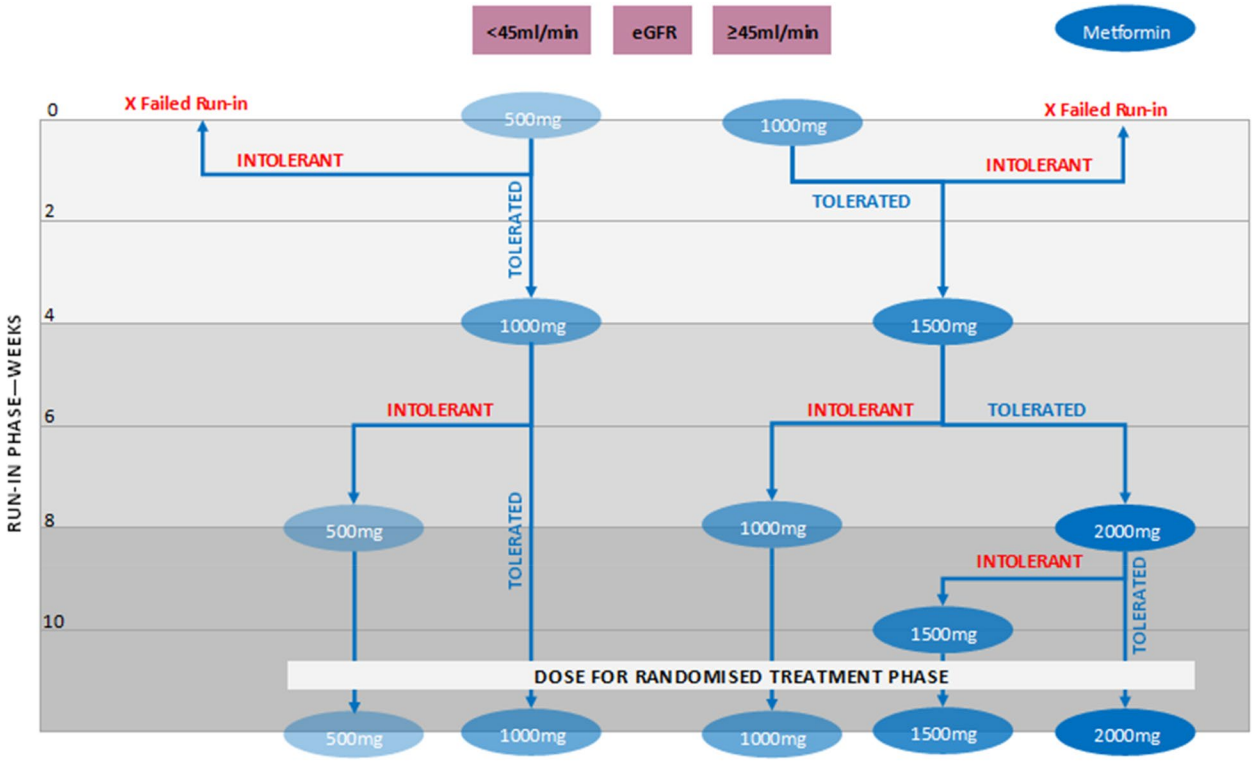

Fig. 2 Study medication active run-in titration overview

run-in phase (during the week 12 visit), participants will be randomly allocated to receive either metformin or matched placebo. Both those randomized to metformin and placebo will receive new tablets. Metformin and placebo will be provided in the same size 500 mg tablets; thus, participants will be taking between 1 and 4 tablets daily based on the dose tolerated and eGFR.

Baseline assessments for the trial phase will be conducted at the week 12 visit, which will also serve as month 0 of the trial phase.

Criteria for discontinuing or modifying allocated interventions {11b}

Medication tolerability will be adjudicated at each study visit by site investigators asking participants how they are tolerating the current dose and if they are experiencing any gastrointestinal side effects. If the dose is not tolerated, adjustments will occur in decrements of 500 mg. If a participant's eGFR falls within the range of 30–44 mL/min/1.73 m^2, the maximal dose will be reduced to 1000 mg/day.

The study medication may be temporarily or permanently discontinued if any of the following are present:

- A serious adverse reaction thought likely due to the study medication
- Requirement to prescribe study-prohibited medication or medication with known interactions with metformin (for example, cimetidine)
- Clinical indication for metformin (for example, a new diagnosis of T2DM)
- Inability to tolerate minimum dosage of study medication
- eGFR < 30 mL/min/1.73 m^2 (as per FDA and TGA guidelines) for a minimum of two measurements in the same week
- Pregnancy or condition (as per treating clinician's discretion) where continuation of the study medication is not considered in the participant's best interests
- Uncontrolled hypertension as defined by systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg after a period of rest, or
- Requested by the participant or their treating physician.

If participants are unable to maintain adequate fluid intake (e.g. due to gastrointestinal upset or dehydration), they will be advised to withhold study medication as metformin may have reduced clearance in this situation and

therefore increased risk of adverse effects. A local guideline on the management of acute illness and prevention of acute kidney injury, such as the Kidney Health Australia (KHA) Sick Day Plan [21], may also be followed.

Study medication may be temporarily stopped for up to 12 weeks. If a participant is to recommence the study drug, the treating physician may elect to either resume the participant at the previously tolerated medication dosage or recommence up-titration as outlined above.

If the study medication is permanently discontinued, the participant will remain in the trial until the final study visit, except where the participant withdraws their consent to participate in the study.

Strategies to improve adherence to interventions {11c}

Face-to-face or remote adherence reminder sessions will be conducted by site staff when the initial study medication dispensing occurs and at each dispensing visit thereafter. Sessions will include:

- The importance of following study guidelines for adherence to study medication as directed
- Instructions on taking study medication including dose timing (particularly that the study product should be taken with the evening meal), storage and what to do in the event of a missed dose
- Notification of the need to return any unused study medication at each study visit to preserve the integrity of the research
- Reinforcement that the study medication may be metformin or placebo
- Importance of calling the clinic if experiencing problems possibly related to study product, including symptoms and lost pills.

Participants will also be asked about any difficulties they are experiencing taking their study medication and will be given the opportunity to ask questions.

Adherence to study medications will be monitored by tablet count at the end of the run-in phase and at each 6-monthly study visit. Participants will return any unused tablets but will not be advised that pill counting is being conducted or used as an adherence measure.

Relevant concomitant care permitted or prohibited during the trial {11d}

All participants will receive their usual CKD management as per the standard of care and local, national and international practice guidelines. This includes, but is not limited to, the management of anaemia, oedema, bone mineral disorder, cardiovascular risk factors/disease and dialysis access/transplant planning.

Blood pressure will be optimized for all participants prior to randomization. The run-in period will target a blood pressure of < 140/90 mmHg, with either up-titration of current medications or the introduction of further anti-hypertensives. This is based on the results of the HALT-PKD trials [22], which demonstrated the beneficial effect of blood pressure control in patients with ADPKD. Newly diagnosed hypertension should be treated with renin–angiotensin–aldosterone system (RAAS) blockers in the first instance unless there is a contraindication. The decision regarding individual blood pressure targets and the choice of anti-hypertensives will be at the discretion of the local treating physician, in line with relevant local and/or international guidelines.

Participants on tolvaptan will be eligible for the study providing therapy has been on a long-term stable dose, as tolvaptan results in an acute GFR decline [23]. Participants will only be eligible if they have been on the medication for at least 6 months, with a stable dose of tolvaptan for the previous 3 months. During the study, sites will be strongly encouraged to maintain the current dosage of tolvaptan, although participants may start, stop, or change dosage. Tolvaptan dose will be recorded over time. Study participants will be stratified by tolvaptan use at randomization.

Provisions for post-trial care {30}

Throughout the trial, participants will maintain usual care under their primary physician. After the trial's completion, this standard of care will be recommended to continue.

Outcomes {12}

The primary outcome measure is the change in eGFR at 2 years from randomization. eGFR will be estimated using the CKD-EPI equation from the serum creatinine concentration collected throughout the study and analysed in local accredited laboratories [24]. Sensitivity analyses will employ the Modification of Diet in Renal Disease (MDRD) equation and cystatin C-based eGFR assessed in a central laboratory.

Secondary outcome measures are:

a) Annualized slope of eGFR
b) A composite outcome comprising a reduction from baseline eGFR of ≥ 30%, kidney failure (defined as an eGFR < 15 mL/min/1.73 m^2) and all-cause mortality
c) Reduction from baseline eGFR of ≥ 30%

d) Kidney failure (defined as an eGFR < 15 mL/min/1.73 m.^{2})
e) All-cause mortality
f) The proportion of participants requiring a dosage adjustment or the introduction of a new anti-hypertensive agent during the treatment period
g) Urine albumin:creatinine ratio
h) Albuminuria (urine albumin:creatinine ratio) category (A1 < 3.39 mg/mmol, A2 3.39–33.9 mg/mmol, A3 > 33.9 mh/mmol) and as a continuous variable
i) Health-related quality of life (QOL) scores measured using EuroQual 5 Dimensions 5 Levels (EQ-5D-5L) questionnaire [25]
j) ADPKD-related pain measured using the ADPKD-PDS [26]
k) Gastrointestinal symptoms measured using the Gastrointestinal Symptom Rating Scale (GSRS) [27]
l) Incidence rates of gastrointestinal symptoms, lactic acidosis, deranged liver function tests, hypoglycaemia, anaemia and vitamin B12 deficiency
m) Healthcare utilization (hospital admissions, non-admitted episodes of primary and specialist care and prescribed medications)
n) Incremental costs and health outcomes (quality-adjusted life year (QALY) and clinically important difference in the primary outcome) of metformin therapy compared to placebo

Exploratory outcome measures will be the change in body weight and body mass index measured using height and weight measures at baseline and 2 years, and duration of interventional product usage. Other exploratory outcome measures may be formulated and proposed, but will only be incorporated with the agreement of the Global Steering Committee (GSC) and upon ethical approval, and then applied with participant consent.

Participant timeline {13}

All participants will be followed up at their respective site according to the schedule in Table 1. There are a total of 13 study visits (telephone, in person or remote). The week 12 visit will mark the end of the run-in phase and month 0 of the trial phase.

Sample size {14}

The study has been powered to detect a 20% reduction in eGFR slope due to metformin, assuming a slope of 6.9 mL/min/1.73 m^2 (over 2 years; standard deviation 12; correlation 0.8) on placebo due to metformin [3, 28, 29], with 80% power at the 5% significance level. Allowing for a 10% loss to follow-up and adjustments for 5% drop-in and 5% drop-out rate, 1174 participants will be recruited.

Recruitment {15}

Participants will be recruited from kidney units that provide a comprehensive kidney specialist service in Australia, the UK, New Zealand, India, Hong Kong, South-East Asia and Europe. Pre-screening will take place at the local recruiting centres, where trained research team members will review the history of centre patients with a diagnosis of ADPKD. Patients who appear to fulfil the inclusion criteria for the study will be approached during their clinic appointments or by mail through a trial invitation letter.

The trial will also be advertised to the ADPKD community through patient-accessible websites, social media and presentations at patient information days. A Consumer advisory board will be consulted and provide input on recruitment strategies. Potential participants will undergo telephone pre-screening by members of the research team at their local recruiting centre, who may (with permission of the potential participant) contact their primary care physician and local hospital if further medical information is required to evaluate eligibility.

Potential participants who meet the eligibility criteria will be provided with a participant information sheet and the opportunity to discuss the trial and ask any questions they may have with the research team. They will then receive a follow-up phone call to determine if they would like to participate.

Assignment of interventions: allocation

Sequence generation {16a}

Eligible participants will be randomly allocated to either metformin or placebo in a 1:1 ratio at the end of the run-in phase. Randomization will be performed using Sealed Envelope (https://www.sealedenvelope.com/), a secure password-encrypted randomization web-based platform. The adaptive allocation algorithm will minimize imbalance across treatment groups in the following variables: use of tolvaptan, CKD stage (stage 2 vs. stage 3), sex, presence/absence of hypertension, study centre and starting dosage of medication as determined at week 10 of the run-in phase.

Concealment mechanism {16b}

When a participant is randomized, the system will release a medication pack number.

Implementation {16c}

An unblinded statistician will generate and upload into the randomization system a list of treatments and their

Table 1 Study visit schedule

Study phase	**Metformin run-in (3 months)**							**Study treatment follow-up (24 months)**						
Time point	**Wk 0**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**	**Wk 10**	**Wk 12/**	**Mth 0**	**Mth 1**	**Mth 3**	**Mth 6**	**Mth 12**	**Mth 18**	**Mth 24**
Location	**Clinic**	**Phone**	**Clinic or remote**	**Phone**	**Clinic or remote**	**Phone**	**Clinic**[†]		**Phone**	**Clinic or remote**	**Clinic or remote**	**Clinic**	**Clinic or remote**	**Clinic**
Screening														
Eligibility	X							X						
Informed consent	X													
Medical history	X													
Clinical assessments														
Concomitant medications	X	X	X	X	X	X		X	X	X	X	X	X	X
Physical examination	X							X				X		X
Blood pressure	X		X		X			X		X	X	X	X	X
GSRS*	X							X				X		X
EQ-5D-5L	X							X				X		X
ADPKD-PDS	X							X				X		X
Adverse events (as required)		X	X	X	X	X		X	X	X	X	X	X	X
Local lab assessments														
Full blood count, biochemistry	X							X				X		X
Vitamin B12 test	X													
Urine assessments	X							X				X		X
Urine osmolality test	X							X				X		X
Creatinine test[‡]			X		X									
Pregnancy test[≠]	X							X				X		X
Central lab assessments[Δ]														
Cystatin C	X							X				X		X
Medication related														
Dispense medication	X							X			X	X	X	
Randomization								X						
Return and count unused medication								X			X	X	X	X

[†] Wk 12 and Mth 0 occur concurrently. [*]Can be conducted at any time only if Participant reports gastrointestinal symptoms. [‡]Creatinine test to determine eGFR during run-in phase to monitor safety. At other time points, eGFR is tested as part of routine local laboratory assessment. [≠]Only for female participants of childbearing age. [Δ]Central lab assessments for sites with sample processing and storage facility

medication pack numbers. The unblinded list will not be accessible to site staff or other trial personnel who will remain blinded.

Assignment of interventions: blinding

Who will be blinded {17a}

Study participants, treating physicians and other care providers, outcome assessors, study investigators and study operation staff (monitors, database managers and blinded statistician) will all be masked to treatment allocation. An unblinded statistician will review treatment allocations to ensure balance across treatment arms and an independent data and safety monitoring board (DSMB) will review unblinded statistical reports during the trial. Table 2 summarizes the trial's blinding.

Procedure for unblinding if needed {17b}

Unblinding is not permitted during the trial except in the event of a serious adverse event related to the study medication. The Coordinating Principal Investigator or delegate will be the main contact for sites to discuss any request for unblinding and will remain blinded. If unblinding is deemed necessary, the time, date and reason will be recorded, and the site investigator will be informed of the allocated treatment via the Randomization platform. Only the minimum number of persons necessary to provide appropriate care for the participant will be made aware of the treatment allocation. The participant will remain in the study and, where possible, continue their allocated study treatment.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Participant samples will be locally collected with subsequent laboratory testing and analysis performed in clinically accredited local laboratories. This will include haematology (full blood count), biochemistry (including liver function tests, serum creatinine and eGFR (CKD-EPI)) and urine tests (albumin:creatinine ratio).

Local laboratories used by participating kidney units must be able to provide documented proof of relevant accreditation. Other participating international centres must provide evidence from the equivalent local laboratory accreditation body.

Central laboratory sample collection is optional and will be used for cystatin C to supplement eGFR calculations. This will only be conducted at sites with both sample processing capacity and available storage facility; samples will be centrifuged and stored at − 80 °C until tested in a central laboratory.

Participants will also be assessed for a range of clinical outcomes using various study instruments and tools, including hypertension status (blood pressure and current anti-hypertensives), participant QOL (EQ-5D-5L) [25], pain assessment (ADPKD-PDS) [30], gastrointestinal symptoms (GSRS) [27], metabolic syndrome (National Cholesterol Education Program Adult Treatment Panel III [NCEP ATP III] criteria) [31], hospitalizations, non-admitted health care utilization and prescribed medicines. Table 1 outlines the schedule of participant assessments.

Plans to promote participant retention and complete follow-up {18b}

Patient input has been sought during the development of the trial protocol through the inclusion of national and international consumer representatives in the investigator team and GSC. There will be ongoing consumer and community engagement via the PKD Australia and PKD international consumer networks. Based on this consumer input, in-clinic study visits have been minimized.

Analyses will be conducted using an intention-to-treat principle. If the study medication is permanently discontinued, the participant will remain in the trial and be followed until the final study visit (except where the participant withdraws consent). Where practical, participants will be asked to complete a final study visit; if this is not possible, every effort will be made to collect data current at the time of cessation. If a participant withdraws their consent to participate, all existing data will be retained in the trial database and no data will be collected past the point of withdrawal.

Data management {19}

IMPEDE-PKD study data will be captured and stored electronically using Research Electronic Data Capture (REDCap) software [32, 33]. Site study staff are responsible for data entry and randomization. The sponsor's Data Management team manages the REDCap accounts where access is only provided to site study staff who signed in the delegation log. A site user manual, quick-reference guides and training are provided to all REDCap users. Individual account access is secured by multi-factor authentication. To promote data quality, data screening is performed regularly to identify data errors. Real-time edit and range checks are implemented in the database. The survey questionnaires—EuroQol 5 Dimensions 5 Levels (EQ-5D-5L), Gastrointestinal Symptom Rating Scale (GSRS) and ADPKD-Pain and Discomfort Scale (ADPKD-PDS)—are collected on paper, and site study staff enter the response data into REDCap. The original paper form is retained in a source document folder on site and may be subject to monitoring to verify data entry accuracy. Investigators are required to maintain all study documentation, including consent documents, ethics committee approvals and correspondence, for a period

Table 2 Summary of trial blinding

Group/individual blinded	Information withheld	Method of blinding
Person assigning participants to groups	Not applicable	Not applicable
Participants	Allocated treatment	Placebo control
Care providers	Allocated treatment	Not told of group assignment
Data collectors and managers	Allocated treatment	Not told of group assignment
Outcome assessors	Allocated treatment	Not told of group assignment
Statisticians	Allocated treatment	Not told of group assignment
Data and Safety Monitoring Board	Not applicable	Not applicable

of 15 years after the closure of the trial or according to relevant national regulations. Thereafter, documents will be shredded and then disposed of, and computer records will be erased. During the EDC data lock, the data are stored in the secure University of Queensland Research Data Manager platform.

Confidentiality {27}

Participants' records and the data generated by the study will be stored confidentially in line with the recommendations of the competent authority and the relevant privacy legislation(s). Any information that may identify a participant will be excluded from data presented in the public arena. All study-related information will be stored securely at the study site. All participant information will be stored in locked filing cabinets in areas with limited access. All laboratory specimens, reports, data collection processes and administrative forms will be identified by a coded identification (ID) number only. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

An exploratory sub-study of genetic/genomic analysis is proposed for Australia. If participants consent to additional analysis, samples will be extracted and frozen at the central lab (Pathology Queensland) for future testing.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

A Statistical Analysis Plan will detail the estimands (e.g. analysis strategy, handling of missing data and intercurrent events) for all outcomes. The primary outcome, change in eGFR, will be analysed using a linear mixed-effects regression model, with the main result being the treatment effect estimate at the final study visit. Secondary and exploratory outcomes with continuous data measured over time (blood pressure, pain intensity/frequency, QOL, weight change) will be analysed using the same method. Repeatedly measured categorical outcomes will be analysed using appropriate generalized linear mixed-effects models. Secondary outcomes measured on a single occasion will be analysed by an appropriate regression model (linear, binary logistic, ordinal logistic, or Cox regression).

Interim analyses {21b}

The protocol specifies three interim analyses, when approximately 25, 50 and 75% of the planned number of participants have completed follow-up. The analyses will use non-binding O'Brien-Fleming boundaries set to control the overall type I error rate at 0.05. The interim analyses will be completed by the unblinded trial statistician. The DSMB will review the reports with the authority to recommend early termination of the trial due to harm or futility.

Methods for additional analyses (e.g. subgroup analyses) {20b}

Potential differences in the effect of treatment on the primary outcome will be assessed for the following subgroups: age (groups), CKD stage (groups), hypertension (groups), *PKD1/2* genotype (groups), htTKV (groups), use of RAAS blockade (RAAS blockade vs. no RAAS blockade), sex (male, female), racial origin (groups), BMI (groups), tolvaptan usage (groups) and presence of metabolic syndrome (no, yes). Subgroup effects will be determined by tests for interaction between the treatment and subgroup variables.

Health economic analysis

In Australia, the cost to the government for outpatient level non-admitted healthcare will be collected by data

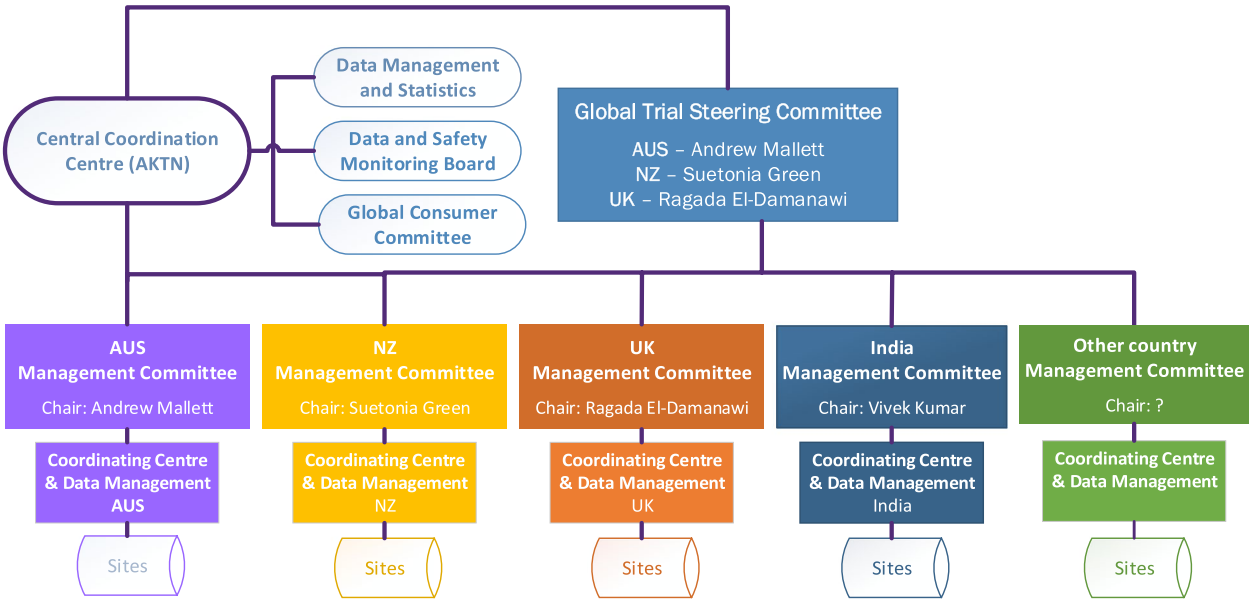

Fig. 3 IMPEDE-PKD clinical trial governance schematic. AKTN, Australasian Kidney Trials Network; AUS, Australia; NZ, New Zealan; UK, United Kingdom

linkage to the Pharmaceutical Benefits Scheme and Medicare Benefits Scheme. The data linkage period for each participant will be from the date of consent to the end of study follow-up period.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

The impact of missing data on the primary analysis is expected to be limited due to (1) randomization requires all covariates and the primary outcome variable to be non-missing at randomization, (2) missing data are monitored regularly and also for DSMB meetings/interim analyses and (3) missing values do not need to be imputed as the primary analysis (mixed-effect regression) does not require participants to have observations at each timepoint. The main reason for missing follow-up data will be due to intercurrent events (protocol deviations, censoring, competing events). The pattern of missing data is expected to be informatively missing (not-at-random) due to intercurrent events such as withdrawal and death. Estimands, specified for each analysis in the Statistical Analysis Plan, will detail the strategies of handling missing data. The primary analysis will follow the 'treatment policy' strategy where intercurrent events are treated as irrelevant for the definition of the treatment effect, while secondary analyses will explore other strategies (using e.g. multiple imputation and tipping-point analysis).

Plans to give access to the full protocol, participant level data and statistical code {31c}

Data sets will be made available to researchers within the IMPEDE-PKD study for analysis of sub-studies and country-specific outcomes after the primary manuscript has been accepted for publication.

For researchers outside the IMPEDE-PKD study, 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.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

An overview of the clinical trial governance structure is provided in Fig. 3. The Australasian Kidney Trials Network (AKTN) will be the Central Coordinating Centre in the initial phase of the trial and will be responsible for convening and reporting to the GSC. The AKTN will also be responsible for developing and maintaining charters for the GSC and DSMB.

The GSC will be responsible for the oversight of the study, including study design; collection, management, analysis and interpretation of data; writing of the final study report; and the decision to submit the report for publication. The GSC will have ultimate authority over these activities.

Each region will have a Trial Management Committee (TMC) led by the Regional Chief Investigator, which will report to the GSC and the Central Coordination Centre. The TMCs will have responsibility for the delivery of the trial in their region and are answerable to the GSC. Each region will have a Regional Coordinating Centre consisting of the Regional Coordinator and Project Lead for that region. The Regional Coordinating Centre will be responsible for managing and supporting the activities of the TMC and regional trial activities.

Consumer involvement

The AKTN Scientific Committee includes two consumer members with lived experience of ADPKD who were responsible for reviewing the initial proposal for this trial and providing feedback that was critical for protocol development. The abovementioned GSC also includes two consumer members to ensure continued consumer oversight of the trial while the New Zealand Coordinating Centre has appointed a consumer Associate Investigator to provide this critical input.

GSC and additional consumer feedback has been sought on participant-facing materials, including those used for recruitment (a trial summary and infographic and AKTN website promotion) and obtaining informed consent. Consumer involvement has also extended to promotion of the trial, via interviews with Australian national news media and the various social media channels utilized by the consumer support society PKD Australia. These consumer-led and oriented avenues will also be utilized for the dissemination of trial results.

Composition of the data monitoring committee, its role and reporting structure {21a}

A global DSMB with four members will be constituted and managed by the central coordination centre and operate in accordance with the IMPEDE-PKD DSMB Charter. Members will have no financial or scientific conflicts of interest with the IMPEDE-PKD trial. The DSMB Chairperson will be a clinician with extensive clinical trials and DSMB experience. The statistician will be an experienced clinical trials statistician with extensive DSMB experience. Two additional members will be nephrologists with clinical trials and DSMB experience.

An unblinded statistician will prepare unblinded statistical reports for meetings of the DSMB. The DSMB will review results from accumulating outcome data with a remit to recommend stopping the trial early for efficacy if, in the opinion of members, this is warranted by the totality of evidence. The DSMB will make recommendations to the GSC Chairperson while maintaining trial confidentiality; the GSC will retain sole decision-making responsibility for modifications to or early stopping of the trial.

Adverse event reporting and harms {22}

Observation and collection of treatment-related adverse events will begin from the time of the first dose of study treatment until the participant's final study visit. Adverse events will be managed as per usual local clinical care practice. For adverse drug reactions, events that the site investigator rates as possibly related to the study medication will be recorded. Specific adverse events of interest related to the study interventional product (metformin) will be recorded, including lactic acidosis and hypoglycaemia. All serious adverse events will be recorded whether related to study medication or not. Further, all adverse events will be collected systematically, coded according to structured language (Medical Dictionary for Regulatory Activities (MedDRA)) and will be reported in resulting trial publications.

Frequency and plans for auditing trial conduct {23}

For the purpose of data validation, the principal investigators will permit a member of the central coordinating centre or its designee to inspect the source data and compare them with the case report forms. Pre-study audits, interim audits and post-study audits may be performed. Notification of these audits will be sent to all investigators in advance.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Any modifications to the protocol, including changes of study objectives, study design, participant population, sample sizes, study procedures, or significant administrative aspects, will require a formal amendment to the protocol. Such amendment will be agreed upon by GSC and approved by the IEC prior to implementation and notified to the health authorities in accordance with local regulations. Changes such as these will be actively communicated through channels such as patient partners in steering committees.

Dissemination plans {31a; 31b}

At the conclusion of the study, the GSC will approve publication and dissemination of results to participants, Principal Investigators and other study staff via a variety of media including a newsletter, peer-reviewed journals, conference presentations and websites.

Authorship will be as per the publication policy (AKTN SOP 1.05, V2.0, 2019) of the trial sponsor, the

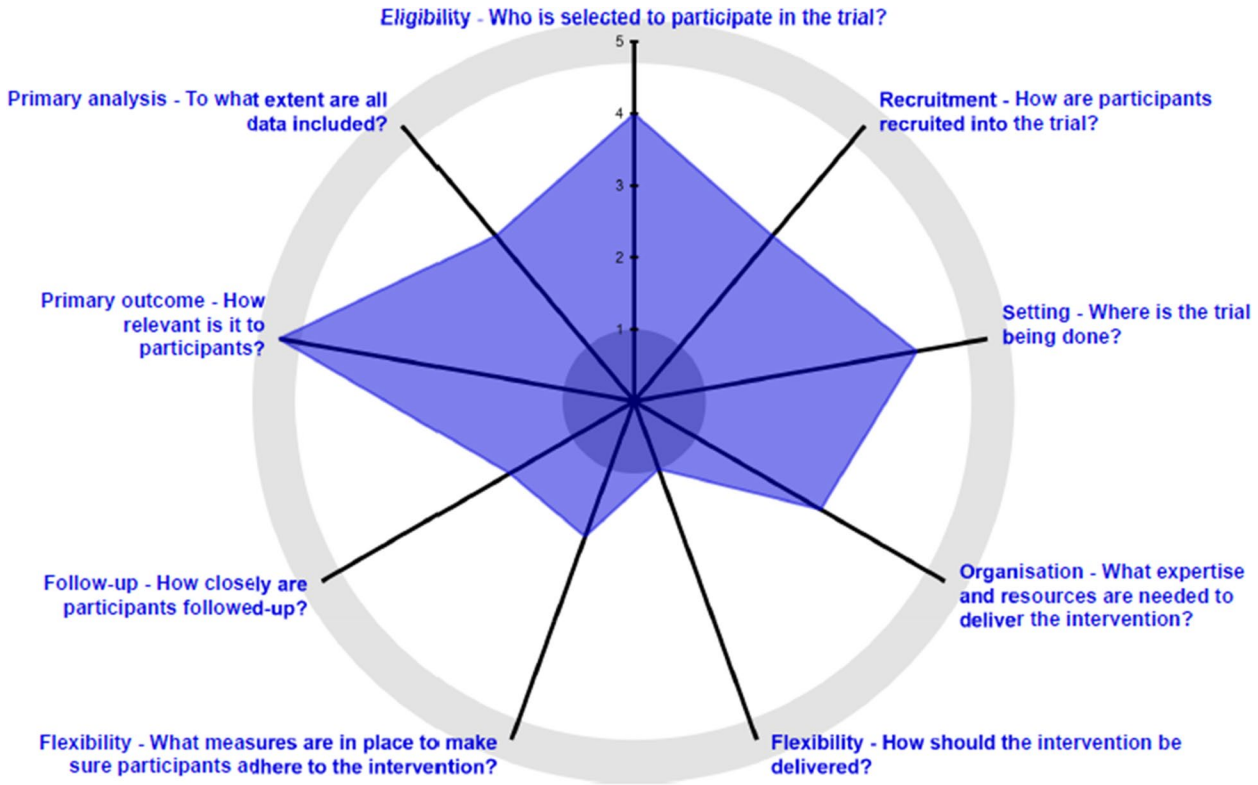

Fig. 4 IMPEDE-PKD Pragmatic Explanatory Continuum Indicator Summary Wheel

Australasian Kidney Trials Network at The University of Queensland. Enacted by the Global Trial Steering Committee via the IMPEDE-PKD Publication Plan (V1.0, 2024), this policy will be incorporated into jurisdictional agreements with the trial sponsor and accord with institutional, journal and International Committee of Medical Journal Editor requirements.

Discussion

There is currently a requirement for more disease-specific interventions that reduce the progression of kidney function decline and improve symptoms and long-term outcomes for patients with ADPKD. IMPEDE-PKD aims to evaluate whether metformin slows the rate of kidney disease progression in ADPKD. Several experimental and limited clinical studies support a potential benefit of metformin for reducing cyst growth and slowing the decline in kidney function in patients with ADPKD [9, 17, 18]. In addition, metformin has a decades-long record of safety in the treatment of T2DM, making it attractive as a long-term treatment for a disease that develops over decades.

While metformin has a well-established safety profile, gastrointestinal disturbances are one of the few dose-limiting side effects that can be minimized through slow titration and administration with food. The design of IMPEDE-PKD titrates metformin dose for all participants during the 12-week run-in phase to minimize dropouts and utilize extended-release preparations of metformin.

The overall extent of the trial's pragmatic or explanatory nature has been assessed using the PRagmatic Explanatory Continuum Indicator Summary version 2 (PRECIS-2) tool [34] (Fig. 4). The trial's pre-established methods to improve and monitor participant adherence, and the number of planned follow-up visits, differ from what a patient may experience in usual care. These methods are considered more explanatory than pragmatic in the domains of flexibility of delivery, flexibility of adherence and follow-up. Given the trial design allows for inclusion of participants on tolvaptan therapy, where other ADPKD studies have excluded this population, the study's eligibility criteria are considered pragmatic. The trial's primary outcome of change in eGFR is relevant to patients with ADPKD and is considered very pragmatic [35].

Two randomized controlled trials evaluating the safety and tolerability of metformin in ADPKD have been published, TAME-PKD [17] and Brosnahan et al. [18]. These studies both reported that metformin was safe and tolerable in patients with ADPKD and

reported numerically smaller average declines in eGFR in metformin-treated participants. Given the small sample sizes, these differences in eGFR decline were not significant; however, they offer promising positive initial results. The question of efficacy has been left open, and IMPEDE-PKD aims to evaluate metformin's efficacy with a larger phase III trial.

Additional attempts to find efficacious therapies to address the current paucity of options to slow ADPKD progression have been challenging. Of note, STAGED-PKD was a two-stage RCT of venglustat that began in 2018 and was halted as it met futility criteria [36]. The FALCON study of bardoxolone methyl in participants with ADPKD was terminated in May 2023 [37]. Furthermore, PREVENT-ADPKD evaluated prescribed water intake over 3 years and found that the intervention did not slow the increase in htTKV [38].

Tolvaptan remains the only disease-modifying therapy that has demonstrated beneficial effects in patients with ADPKD. Tolvaptan was first registered in Japan in 2014, later being registered in America, Europe and Australia for patients with rapidly progressing ADPKD. Participants on tolvaptan are eligible to enrol in IMPEDE-PKD, though they will need to be stabilized on therapy before commencement of the trial. Initial stratification of participants by tolvaptan use may help to address the question of whether concurrent metformin and tolvaptan is superior to metformin monotherapy.

Based on pilot and experimental data, metformin warrants evaluation as an effective, safe and affordable therapy to slow the progression of kidney function decline in ADPKD, possibly either alone or in addition to tolvaptan therapy. Given the current lack of options for slowing ADPKD progression, this would be a welcome addition to treatment regimens.

Trial status

The current protocol version, 3.2, was approved in April 2024. Participant recruitment is currently underway in Australia and New Zealand and is expected to commence in other international jurisdictions throughout 2025.

Special Acknowledgement

This trial and protocol are dedicated to the memory of Tess Harris and Godela Brosnahan who both substantially contributed to the IMPEDE-PKD trial, its protocol and this protocol article over many years.

Appendix

List of Collaborators

IMPEDE-PKD Global Steering Committee: Andrew J. Mallett (Chair), Townsville Hospital and Health Service, Australia; Ragada El-Damanawi (Deputy Chair), Sheffield Kidney Institute, United Kingdom; Godela Brosnahan, University of Colorado Denver, USA; Michel Chonchol, University of Colorado, Denver, USA; Flavia Galletti, PKD International; Loreto Gesualdo, University of Bari, Italy; Charmaine Green; Suetonia Green, University of Otago, New Zealand; Tess Harris, PKD International; Carmel Hawley, The Univrsity of Queensland, Australia; Kirsten Howard, The Leeder Centre for Health Policy, Economics and Data, Faculty of Medicine and Health, The University of Sydney; Martin Howell, The Leeder Centre for Health Policy, Economics and Data, Faculty of Medicine and Health, The University of Sydney, Australia; Audrey Hughes, Polycystic Kidney Disease Charity; Vivekanand Jha, The George Institute for Global Health, India & the University of New South Wales Australia; David W Johnson, The University of Queensland, Australia; Francois Jouret, University of Liege Academic Hospital,, Belgium; Vivek Kumar, Department of Nephrology, Postgraduate Institute of Medical Education and Research, Chandigarh, India; Becky Mingyao Ma, University of Hong Kong; Amali Mallawaarachchi, Clinical Genetic Service, Institute of Precision Medicine and Bioinformatics, Royal Prince Alfred Hospital, Australia; Steve McTaggart, Queensland Children's Hospital, Queensland, Australia; Andrew J. Mallett, The University of Queensland, Australia; Djalila Mekahli, PKD Research Group, Laboratory of Ion Channel Research, Department of Cellular and Molecular Medicine, KU Leuven, Belgium;; Roman Müller, Department II of Internal Medicine and Center for Molecular Medicine, University of Cologne, Faculty of Medicine and University Hospital Cologne, Germany;; Ron Perrone, Tufts Medical Center, Tufts University School of Medicine, USA; Carol Pollock, Royal North Shore Hospital, Australia; Gopala Rangan, Westmead Institute for Medical Research, The University of Sydney, Australia; Stephen Seliger, University of Maryland School of Medicine, USA; Vicente Torres, Mayo Clinic Translational Polycystic Kidney Disease Center, USA; Andrea K Viecelli, Princess Alexandra Hospital, Australia.

Abbreviations

ADPKD	Autosomal dominant polycystic kidney disease
ADPKD-PDS	ADPKD-Pain and Discomfort Scale
AMPK	AMP-activated protein kinase
CFTR	Cystic fibrosis transmembrane conductance regulator
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease—Epidemiology Collaboration
DSMB	Data and Safety Monitoring Board
eGFR	Estimated glomerular filtration rate
EQ-5D-5L	EuroQual 5 Dimensions 5 Levels
FDA	Food and Drug Administration

GSC	Global Steering Committee
GSRS	Gastrointestinal Symptom Rating Scale
htTKV	Height-adjusted total kidney volume
IEC	Independent Ethics Committee
KHA	Kidney Health Australia
MDRD	Modification of Diet in Renal Disease
NYHA	New York Heart Association Functional Classification
QALY	Quality-adjusted life year
PRECIS-2	PRagmatic Explanatory Continuum Indicator Summary version 2
RCT	Randomized controlled trial
REDCap	Research Electronic Data Capture
T2DM	Type 2 diabetes mellitus
TGA	Therapeutic Goods Association
TKV	Total kidney volume
TMC	Trial Management Committee
XR	Extended release

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-09010-6.

Supplementary Material 1.

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Australasian Kidney Trials Network Operational Team: Charani Kiriwandeniya, Pushparaj Velayudham, Liza A Vergara, Gabor Mihala, Misa Matsuyama, Peta-Ann Paul Brent, Laura E Hickey.
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Italy: Giovanni Piscopo, Department of Nephrology, Dialysis and Transplantation AOUC Policlinico di Bari
See Appendix for List of Collaborators who are members of the IMPEDE-PKD Global Steering Committee

Authors' contributions
All authors were involved in study design and concept. AJM is the trial's Lead Principal Investigator. KS led the writing of this manuscript. All authors contributed to revising the manuscript and read and approved the final version.
Authors' information.
AV is supported by an NHMRC Emerging Leadership (EL1) Investigator Grant (APP1196033) and a Queensland Advancing Clinical Research Fellowship. AJM is supported by a Queensland Advancing Clinical Research Fellowship and led a successful application for the commencement of IMPEDE-PKD (MRFF, MRF1199853; PKD Australia, 2018 Project Grant). DWJ is supported by an NHMRC Leadership (L3) Investigator Grant (APP1194485).

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Data availability
Data sets will be made available to researchers within the IMPEDE-PKD Study for analysis of sub-studies and country-specific outcomes after the primary manuscript has been accepted for publication. For researchers outside the IMPEDE-PKD Study, 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.

Declarations

Ethics approval and consent to participate {24}
Ethics approval for the IMPEDE-PKD trial was obtained in Queensland, Australia, from Metro South Hospital and Health Service Human Research and Ethics Committee (approval reference HREC/2021/QMS/70436). The study has received local governance approvals at each of the participating sites. Each participating jurisdiction will ensure relevant regulatory and ethical approvals are received prior to the trial beginning in that country.

Consent for publication
Consent for publication is not applicable since there are no identifying images or other personal or clinical details of participants presented. A model participant information sheet and consent form are provided.

Competing interests {28}
AJM has previously received research funding from Sanofi-Genzyme, been a member of a Medical Advisory Board for Otsuka Australia, and been clinical trial local site Principal Investigator for Reata, Sanofi-Genzyme and Dicerna. AJM is supported by a Queensland Government Advancing Clinical Research Fellowship. DWJ has received consultancy fees, research grants, speaker's honoraria and travel sponsorships from Baxter Healthcare and Fresenius Medical Care, consultancy fees from Astra Zeneca, Bayer and AWAK, speaker's honoraria from ONO and Boehringer Ingelheim & Lilly, and travel sponsorships from Ono and Amgen. VJ reports consulting fee/honoraria from Bayer, Astra Zeneca, Boehringer Ingelheim, Biocryst, Vera, Visterra, Otsuka, Novartis, Astra Zeneca, Chinook, Biocryst and Alpine under the policy of all payments going to the organization. The other coauthors declare no relevant conflicts of interest.

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