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Implementation of Metformin theraPy to Ease DEcline of kidney function in Polycystic Kidney Disease (IMPEDE-PKD): randomised placebo-controlled trial

Submission date
04/04/2025

Recruitment status
Not yet recruiting

Registration date
30/05/2025

Overall study status
Ongoing

Last Edited
01/07/2025

Condition category
Urological and Genital Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Autosomal dominant polycystic kidney disease (ADPKD) is a leading cause of kidney failure. This inherited condition causes the development of fluid-filled sacs called cysts within the kidneys. Cysts grow over time, damaging and replacing healthy kidney tissue, stopping them from being able to filter the blood effectively. More than 70% of those affected require kidney replacement therapy by the age of 58 years. Currently, there is only one treatment available which isn't suitable for everyone and can cause troublesome side effects.
Metformin is a low-cost, widely available medication, safely used to treat diabetes for decades. Recent research has shown metformin blocks two key signals that drive kidney cyst growth, and that it is safe and well tolerated in people with ADPKD. The main side effects are diarrhoea and bloating. These occur in 30% and usually settle within a few weeks and may be alleviated by taking metformin with food. 60% of ADPKD patients experience chronic pain, significantly impacting their lives. The UK trial includes a questionnaire to find out more about the pain and if metformin helps by slowing cyst growth.

Who can participate?
ADPKD patients aged 18-70 years

What does the study involve?
During an initial 12-week run-in phase all participants will take metformin daily for 10 weeks to find the optimum acceptable dose for them. All participants will wash out for the final 2 weeks of the run-in. Those who can successfully take metformin at the end of the run-in phase will be randomly divided into two groups. Each group will be assigned to either metformin or placebo 'dummy' tablets. The assigned tablet(s) will be taken every day for the next 2 years. Participants will complete questionnaires, provide blood and urine samples, undergo non-invasive physical examinations and blood pressure measurements to ensure their safety and help answer the study's research questions.

What are the possible benefits and risks of participating?
It cannot be guaranteed that the trial will help participants, but the information we collect may improve our ability to treat ADPKD patients in the future.
Participants may experience adverse effects from metformin. Use of the prolonged release formulation and dosing requirements to take trial medication with food reduces gastrointestinal side effects associated with metformin. Dose reductions/adjustments, in line with the minimum dosing requirements for the trial, are permitted according to participant tolerance and/or where clinically indicated. Adverse events of special interest and serious adverse events are recorded from consent to 4 weeks after the last dose of trial medication.
A run-in phase must be completed prior to and does not guarantee randomisation into the treatment phase. Participants are informed of this via the information sheet. The run-in phase identifies participants who are unable to tolerate metformin and for whom inclusion in the main trial would jeopardise data integrity and not be in their best interests.
Additional hospital visits beyond those expected as part of usual care are required for trial participation. Where possible, study visits have been designed to coincide with standard clinic appointments. Participants may be reimbursed for their travel as outlined in the site agreement. Remote visits by phone call have been incorporated where permissible.
Women of childbearing potential are required to use highly effective contraception during and for one month after trial participation, and cannot plan to be pregnant for 3 years to participate. Pregnancy affects kidney blood flow and measures of kidney function so the risk of pregnancy in participants must be managed. All forms of highly effective contraception are permitted.
Safety bloods may cause some discomfort and/or bruising, and must be fasted at the screening visit. Study-specific samples are kept to minimal levels possible and standard care results may be used where they meet trial protocol requirements.
In total, trial participation occurs over 27 months (12-week run-in phase and 24-month treatment phase). Study visits, particularly in the treatment phase, are kept to a minimum to reduce participant burden as much as possible, while allowing adequate data collection to answer the trial's research questions. Outside of completing trial visits and taking the study medication, participants can continue their usual activities unaffected.
Questionnaires take around 15-20 minutes to complete. Responses are collected at 4 study timepoints only. The APAT may be completed electronically where participants prefer. Repetition has been avoided as much as possible. The patient engagement working group collaborated with the Chief Investigator to develop the APAT.

Where is the study run from?
Norwich Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?
April 2025 to April 2029

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?
1. Megan Jones, megan.l.jones@uea.ac.uk
2. Dr Ragada El-Damanawi, ragada.eldamanawi1@nhs.net

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1010940

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
STH21643, CPMS 55849

Study information

Scientific Title
Implementation of Metformin theraPy to Ease DEcline of kidney function in Polycystic Kidney Disease (IMPEDE-PKD): randomised placebo-controlled trial

Acronym
IMPEDE-PKD

Study objectives
Primary objectives:
To see if metformin, a common diabetes medication, can help slow down kidney damage in people with autosomal dominant polycystic kidney disease (ADPKD) (a type of kidney disease), compared to those who take a placebo (a harmless pill with no active drug).

In addition, the main objective of the UK trial is to see if metformin changes average pain severity for people with ADPKD compared to those who take the placebo.

Secondary objectives (looked at over 24 months):
1. To see if metformin can slow down how quickly kidney disease progresses in people with ADPKD by looking at other health markers like kidney size, blood pressure, protein in urine, and the development of kidney failure
2. To check if metformin is safe and well-tolerated over a long period in people with ADPKD
3. To see how metformin affects quality of life and pain related to ADPKD

UK-specific secondary objectives:
1. To measure changes in people's use of pain medication over 24 months using a specific scoring system
2. To map where the pain(s) is experienced using whole body maps and to see if this changes over 24 months
3. To see if the type of kidney pain people experience changes over 24 months using a specific scoring system

Exploratory objectives:
1. To see how body weight and Body Mass Index (BMI) change over 24 months from the start of the study

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 29/05/2025, North East - Newcastle & North Tyneside 2 Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8086; newcastlenorthtyneside2.rec@hra.nhs.uk), ref: 25/NE/0077

Study design
Double-blind randomized placebo-controlled parallel-group trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Safety, Efficacy

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Autosomal dominant polycystic kidney disease (ADPKD)

Interventions
IMPEDE-PKD is a Phase III, international, prospective, multicentre, double-blind, parallel group, placebo-controlled, randomised trial. Randomisation will be by an adaptive allocation algorithm designed to minimise imbalance across treatment groups in the following variables: use of tolvaptan (yes/no), CKD stage (stage 2/stage 3), sex, presence/absence of hypertension, study centre, and starting dosage of trial medication as determined at Week 10 of the run-in phase. Randomisation is performed via the global randomisation system through Sealed Envelope.

Participation occurs over two phases: the run-in phase (12 weeks) and the treatment phase (24 months). There are 13 study reviews; some occur by phone call, and others require a hospital visit.

Patients will be screened by recruiting site teams, and potentially eligible participants invited to consent to the trial following a study consultation with an authorised member of the site team. A screening visit (week 0) at site comprising: consent; medical history; concomitant medication check; eligibility check; physical examination; blood pressure; fasted safety bloods (renal function tests including glucose/liver function tests/full blood count/lactate dehydrogenase /HbA1c/vitamin B12. For women of child-bearing potential bloods will also include a pregnancy test); urine tests (specific gravity/pH/blood/protein/glucose/urine albumin:creatinine ratio/urine osmolality); questionnaires (Gastrointestinal Symptom Rating Scale [GSRS]/EQ-5D-5L/APAT (including the Autosomal Dominant Polycystic Kidney Disease Pain and Discomfort Scale [ADPKD-PDS]); and run-in IMP dispense.

Eligible participants will attempt a 12-week run-in phase; metformin (as 500 mg prolonged-release oral tablets) will be taken for 10 weeks, followed by a 2-week washout. Participants will commence either 500 mg or 1000 mg once daily, depending on kidney function measured using eGFR. The metformin dose will be titrated at 4-week intervals (week 4 and week 8) during the run-in phase to identify the participant’s maximum tolerated dose, not exceeding 1000 mg or 2000 mg, depending on eGFR.

At weeks 2/6/10 of the run-in phase, participants will complete a phone call review to check concomitant medication and adverse events.

At weeks 4 and 8, participants will attend the site for: concomitant medication check; blood pressure; adverse events check; creatinine blood test; and titration of the run-in IMP dose, where applicable.

Those that successfully tolerate a minimum of either 500 mg or 1000 mg daily at week 10 of the run-in phase will then be randomised at Week 12/Month 0 in a 1:1 ratio to receive metformin or matched placebo. Participants will take between one and four 500 mg tablets (metformin or placebo) orally once daily for 24 months. Randomisation will occur after completion of baseline

assessments at the site: run-in IMP adherence check; return of any unused run-in IMP; eligibility check; concomitant medication check; physical examination; blood pressure; safety bloods (renal function tests including glucose/liver function tests/full blood count/lactate dehydrogenase /HbA1c. For women of child-bearing potential bloods will also include a pregnancy test); urine tests (specific gravity/pH/blood/protein/glucose/urine albumin:creatinine ratio/urine osmolality); questionnaires (GSRS/EQ-5D-5L/APAT); and dispense of a 6 month supply of (blinded) treatment phase IMP.

The treatment phase occurs over 6 visits. Where safety bloods are not taken, results of standard care creatinine and eGFR tests will be reviewed.

At month 1, participants will complete a phone call review to check concomitant medication and adverse events.

At months 3/6/18, participants will attend the site to check concomitant medication, adverse events, and blood pressure. At months 6 and 18, participants will receive another 6-month supply of (blinded) treatment phase IMP.

At month 12, participants will attend the site to: check concomitant medication; check adverse events; blood pressure; physical examination; safety bloods (renal function tests including glucose/liver function tests/full blood count/lactate dehydrogenase/HbA1c. For women of child-bearing potential bloods will also include a pregnancy test); urine tests (specific gravity/pH /blood/protein/glucose/urine albumin:creatinine ratio/urine osmolality); questionnaires (GSRS /EQ-5D-5L/APAT); and dispense of a 6 month supply of (blinded) treatment phase IMP.

At month 18, participants will attend the site to check concomitant medication, adverse events and blood pressure, and dispense a final 6-month supply of (blinded) treatment phase IMP.

At month 24, participants will attend the site for a final time to: check concomitant medication; check adverse events; blood pressure; physical examination; safety bloods (renal function tests including glucose/liver function tests/full blood count/lactate dehydrogenase/HbA1c. For women of child-bearing potential bloods will also include a pregnancy test); urine tests (specific gravity/pH/blood/protein/glucose/urine albumin:creatinine ratio/urine osmolality); questionnaires (GSRS/EQ-5D-5L/APAT); and return any unused treatment phase IMP.

Intervention Type
Drug

Pharmaceutical study type(s)
Therapy

Phase
Phase III

Drug/device/biological/vaccine name(s)
Metformin hydrochloride

Primary outcome measure
Global primary outcome measure: change in eGFR, taken from renal function blood tests at baseline, 12 months and 24 months post-randomisation, measured using the CKD-EPI equation

UK-specific primary outcome measure: pain severity measured using an 11-point numerical rating system of average pain over the last 14 days in the ADPKD Pain Assessment Tool (APAT) at baseline, 12 months and 24 months post-randomisation

Secondary outcome measures

Global secondary outcome measures:
1. Annualised slope of eGFR calculated from renal function blood tests at baseline, 12 months and 24 months post-randomisation
2. A composite outcome comprising a reduction from baseline eGFR of more than or equal to 30%, kidney failure (defined as an eGFR <15 ml/min/1.732), and all-cause mortality taken from renal function blood tests and/or healthcare records at baseline, 12 months and 24 months post-randomisation
3. Reduction from baseline eGFR of more than or equal to 30% calculated from renal function blood tests at baseline, 12 months and 24 months post-randomisation
4. Kidney failure (defined as an eGFR <15 ml/min/1.732) calculated from renal function blood tests at baseline, 12 months and 24 months post-randomisation
5. All-cause mortality taken from survival data at 24 months
6. The proportion of participants requiring a dosage adjustment or the introduction of a new anti-hypertensive agent during the treatment period from PI or sub-investigator assessment at 24 months
7. Urine albumin:creatinine ratio taken from urine tests at baseline, 12 months and 24 months post-randomisation
8. Albuminuria (urine albumin:creatinine ratio) category A1 <3.39 mg/mmol, A2 3.39-33.9 mg /mmol, A3 >33.9 mg/mmol, and as a continuous variable taken from urine tests at baseline, 12 months and 24 months post-randomisation
9. Health-related quality of life (HRQoL) measured using EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) questionnaire at baseline, 12 months and 24 months post-randomisation
10. ADPKD-related pain scores measured using the ADPKD-PDS at baseline, 12 months and 24 months post-randomisation
11. Gastrointestinal symptoms measured using the GSRS at baseline, 12 months and 24 months post-randomisation
12. Incidence of gastrointestinal symptoms, lactic acidosis, deranged liver function tests, hypoglycaemia, anaemia, and vitamin B12 deficiency (rate per 100-person years) from adverse event data at 24 months

UK-specific secondary outcome measures:
1. Analgesic burden measured using the Medication Quantification Score Version III (MQS VIII) completed at baseline, 12 months and 24 months post-randomisation
2. Sites of pain according to whole body maps in the APAT completed at baseline, 12 months and 24 months post-randomisation
3. Kidney pain severity measured using a 5-point Numerical Rating Scale (NRS) of dull kidney pain over the last 7 days in the APAT completed at baseline, 12 months and 24 months post-randomisation
4. Kidney pain interference measured using a 5-point NRS of dull kidney pain interference over the last 7 days in the APAT completed at baseline, 12 months and 24 months post-randomisation
5. Quality of kidney pain measured by the APAT completed at baseline, 12 months and 24 months post-randomisation

Overall study start date

02/04/2025

Completion date
01/04/2029

Eligibility

Key inclusion criteria
To be eligible to participate in this trial, patients must satisfy ALL of the inclusion criteria:
1. Able to provide informed consent
2. Aged 18-70 years
3. Diagnosis of ADPKD based on radiological +/- genetic criteria as per standard clinical practice in the UK
4. eGFR ≥38ml/min/1.732 and <90m/min/1.73m2. eGFR measured within the previous 6 months will be used for initial screening and run-in enrolment/dosing. The eGFR measured in the week 8 bloods will determine eligibility to proceed with treatment phase enrolment and randomisation.
5. For participants on tolvaptan therapy, they need to be on it for at least 6 months with a stable dose for at least 3 months.
6. Participants MUST have either or both of:
6.1. One or more risk factors for disease progression from the following:
6.1.1. Bilateral kidney length more than or equal to 16.5 cm or
6.1.2. Total Kidney Volume (TKV) more or equal to 750 mL or height-adjusted Total Kidney Volume (htTKV) more or equal to 600 mL/m2 or
6.1.3. Mayo class 1C/D/E or
6.1.4. Pro-PKD score more than or equal to 6
OR
6.2. Evidence of active progression defined by one of the following:
6.2.1. Decline in eGFR more than or equal to 5 ml/min/1.73 m2 in 1 year or
6.2.2. Decline in eGFR more than or equal to 3 ml/min/1.73 m2 per year over 5 years or more, or
6.2.3. Increase in TKV or htTKV of more than or equal to 5% per year on at least two measurements in the past year, excluding any initial eGFR effect over the initial 3 months of tolvaptan commencement (if applicable)

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
70 Years

Sex
Both

Target number of participants
UK sample size: 300; global sample size: 1174

Key exclusion criteria

1. Diabetes mellitus (as per American Diabetes Association definition) or other systemic conditions that may cause Chronic Kidney Disease (CKD) independent of Polycystic Kidney Disease (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 (NYHA) III or IV
4. Non-polycystic liver disease, including but not limited to:
4.1. Liver enzymes (ALT, AST or Total Bilirubin) >2 times the upper limit of normal
4.2. In the case of Gilbert's Syndrome; liver enzymes (ALT, AST) >2 times the upper limit of normal and/or total bilirubin >3 times the upper limit of normal
4.3. Child-Pugh classification score ≥5
5. Any contraindication to metformin and/or placebo excipients
6. Currently taking metformin
7. Pregnancy or breastfeeding, or planning to get pregnant in the next 3 years
8. Women of childbearing potential not using a highly effective form of contraception
9. Comorbidities with contraindication for metformin use or potential to contaminate trial outcomes (specifically active cancer, and/or history of other solid organ transplantations (kidney, heart, liver, lung, bowel), and/or presence of stoma
10. Active chronic obstructive pulmonary disease (COPD), active inflammatory bowel disease (IBD), or other active disease resulting in current or expected requirement for systemic steroid therapy during the trial follow-up period
11. History of dialysis
12. Participation in the active phase of another CTIMP, or within 4 weeks or 5 half-lives of last study drug administration (whichever is longer)

Date of first enrolment
01/09/2025

Date of final enrolment
30/09/2028

Locations

Countries of recruitment
Australia

Canada

England

Hong Kong

India

Italy

New Zealand

Northern Ireland

Scotland

United Kingdom

Study participating centre
Northern General Hospital
Herries Road
Sheffield
United Kingdom
S5 7AU

Study participating centre
Norfolk & Norwich University Hospital
Colney Lane
Colney
Norwich
United Kingdom
NR4 7UY

Study participating centre
Royal Devon and Exeter Hospital
Royal Devon & Exeter Hospital
Barrack Road
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EX2 5DW

Study participating centre
Kings College Hospital
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De Crespigny Park
Denmark Hill
London
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SE5 8AB

Study participating centre
Churchill Hospital
Churchill Hospital
Old Road
Headington

Oxford
United Kingdom
OX3 7LE

Study participating centre
Salford Royal Hospital
Stott Lane
Eccles
Salford
United Kingdom
M6 8HD

Study participating centre
Royal Free Hospital
Pond Street
London
United Kingdom
NW3 2QG

Study participating centre
The Royal London Hospital
Alexandra House
London
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Study participating centre
University Hospital Birmingham
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B15 2TH

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Freeman Road
High Heaton
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NE7 7DN

Study participating centre
Nottingham City Hospital
Hucknall Road
Nottingham
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NG5 1PB

Study participating centre
Royal Stoke University Hospital
Newcastle Road
Stoke-on-trent
United Kingdom
ST4 6QG

Study participating centre
St Helier Hospital
Wrythe Lane
Carshalton
United Kingdom
SM5 1AA

Study participating centre
St Lukes Hospital
Little Horton Lane
Bradford
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BD5 0NA

Study participating centre
Royal Preston Hospital
Sharoe Green Lane
Fulwood
Preston
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PR2 9HT

Study participating centre

Doncaster Royal Infirmary
Armthorpe Road
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DN2 5LT

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Aintree University Hospital
Fazakerley Hospital
Lower Lane
Liverpool
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L9 7AL

Study participating centre
Leicester General Hospital
Gwendolen Road
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LE5 4PW

Study participating centre
Daisy Hill Hospital
5 Hospital Rd
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BT35 8DR

Study participating centre
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Study participating centre
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BT16 1RH

Study participating centre
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45 Bush Rd
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United Kingdom
BT41 2RL

Study participating centre
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IV2 3UJ

Sponsor information

Organisation
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Royal Hallamshire Hospital
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Sponsor type
Hospital/treatment centre

Website
http://www.sth.nhs.uk/

ROR
https://ror.org/018hjpz25

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Peer-reviewed scientific journals
2. Conference presentation
3. Publication on website
4. Submission to regulatory authorities
5. Other

Intention to publish date
01/04/2030

Individual participant data (IPD) sharing plan
Data requests to be sent to Megan Jones megan.l.jones@uea.ac.uk and/or Dr Ragada El-Damanawi ragada.eldamanawi1@nhs.net. Datasets will be anonymised and available after the primary manuscript has been accepted for publication for 25 years after the trial closes. Participants consent to the sharing of anonymised data with other researchers at enrolment. Participants are assigned a Participant IDentification (PID) at consent and only the recruiting site (and NCTU trial team until the end of the trial) can identify the participants. Requests to access trial data must be made in writing for consideration by the UK Trial Management Group and/or the Trial Steering Committee via the contacts listed.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 1.1	08/05/2025	30/05/2025	No	Yes