

# Preventing Kidney Injury Using Carbon Dioxide (KID Trial): Trial Protocol for a Multicentre Randomised Controlled Trial

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## **Authors and Contributors:**

Athanasios Saratzis<sup>1</sup>, Neha Rasheed<sup>2</sup>, Dania Aguirre<sup>2</sup>, Patrick Coughlin<sup>3</sup>, Athanasios Diamantopoulos<sup>4</sup>, Lindsay Bearne<sup>5</sup>, Nicholas Selby<sup>6</sup>, Cassandra Brookes<sup>2</sup>, Shaun Barber<sup>2</sup>, Carla Richardson<sup>2</sup>, Hannah Gilbert<sup>1</sup>, Roland Schueller<sup>2</sup>, Despoina Apergi<sup>7</sup>, Keith Harris<sup>7</sup>

## **Affiliations**

1. Department of Cardiovascular Sciences, University of Leicester
2. Leicester Clinical Trials Unit, University of Leicester
3. Leeds Vascular Institute, Leeds General Infirmary
4. Guy's and St Thomas' NHS Foundation Trust
5. St George's University of London
6. Centre for Kidney Research and Innovation, University of Nottingham
7. Patient and Public Involvement Representatives

## **Corresponding Author:**

Professor Athanasios Saratzis (Chief Investigator)

Email: [as875@leicester.ac.uk](mailto:as875@leicester.ac.uk); Telephone: 0044 01162523190

Address: NIHR Leicester Biomedical Research Centre; BHF Cardiovascular Research Facility; Leicester; LE39QP; United Kingdom.

## **KEYWORDS**

Peripheral arterial disease, endovascular revascularisation, chronic kidney disease, CO<sub>2</sub> injector, contrast medium, acute kidney injury, iodine-based contrast medium, carbon dioxide, nephrotoxic.

## **Trial registration**

IRAS ID: 340062; ISRCTN: 23564393; Registration date: 29 November 2024; Funder's reference number: NIHR206198

## **ABSTRACT**

### **Introduction**

Peripheral Arterial Disease (PAD) commonly co-exists with Chronic Kidney Disease (CKD). Patients with symptomatic PAD often require endovascular revascularisation to relieve pain or salvage limbs. However, the iodinated intra-arterial contrast routinely used in these procedures is nephrotoxic, placing patients with CKD at increased risk of Acute Kidney Injury (AKI) and long-term renal decline. Carbon dioxide (CO<sub>2</sub>) delivered via automated injection is a potential alternative imaging contrast medium. This trial will evaluate whether using CO<sub>2</sub> instead of iodinated contrast reduces the risk of AKI and short-term renal function decline in this high-risk group.

### **Methods and analysis**

This is a multicentre, open-label, prospective randomised controlled trial (RCT) across six secondary-care NHS vascular surgery centres. A total of 174 patients with PAD and

CKD undergoing endovascular intervention will be randomised 1:1 to receive iodinated contrast (standard of care) or CO<sub>2</sub> via automated injector (Angiodroid™). All perioperative care will follow local NHS protocols.

The primary outcome is log serum creatinine at 2, 30, and 90 days post-procedure. Key secondary outcomes include: incidence and severity of AKI within 48 hours post-procedure, major adverse kidney events (death, dialysis, or >25% eGFR decline) by 90 days, inpatient length of stay, procedural pain, quality of life, procedural success, re-interventions, acceptability and feasibility (patient/practitioner questionnaires) of using CO<sub>2</sub>, and cost-effectiveness (healthcare resource use analysis). A mixed-methods process evaluation will be undertaken with patients and clinicians.

### **Ethics and dissemination**

The trial has been approved by an NHS ethical review committee (24/WA/0332) and patients have been involved in trial design. Findings will be disseminated to participants, clinicians, and the wider public through patient groups, lay summaries, social media, conferences, peer-reviewed journals, and NHS policy channels.

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### **Strengths and limitations of this study**

- This is a multicentre, pragmatic randomised controlled trial conducted across six NHS vascular centres, enhancing generalisability of findings.
- The trial design incorporates both clinical and health economic analyses, allowing evaluation of effectiveness and cost-effectiveness within routine NHS care.
- Outcome assessments are based on objective, routinely collected biochemical measures, reducing measurement bias.
- A mixed-methods process evaluation enables detailed assessment of feasibility, acceptability, and implementation factors for CO<sub>2</sub> angiography.
- The open-label design may introduce performance bias, although objective renal outcomes minimise its potential impact.

## INTRODUCTION

### Background and Rationale

When revascularising the lower limbs of people with Peripheral Arterial Disease (PAD), iodine-based contrast medium is used to visualise arteries and allow operators to perform the procedure(1, 2). This contrast medium, being nephrotoxic, can contribute to acute kidney injury (AKI), the most common complication after these procedures. One way to minimise AKI risk may be to use carbon dioxide (CO<sub>2</sub>) as a contrast medium, which is not nephrotoxic and does not contain iodine (CO<sub>2</sub> is used widely in other invasive procedures e.g., laparoscopy)(3). The value of using CO<sub>2</sub> to reduce AKI in this context, however, has not been tested in a randomised setting.

Acute kidney injury is the most common complication of endovascular (minimally invasive) revascularisation for PAD, especially in patients with pre-existing Chronic Kidney Disease (CKD)(1). Post-intervention AKI in this context is strongly and independently associated with higher mortality, cardiovascular events, and NHS costs, in the short and long term(4, 5). One of the key reasons why these patients develop AKI is the use of iodinated contrast medium, which is injected to visualise their arteries(6). CO<sub>2</sub> can also be used as a contrast medium during such procedures; CO<sub>2</sub> is safe to be injected intra-arterially and not nephrotoxic(7-9). The use of CO<sub>2</sub>, however, can be challenging due to the complexity of the procedure, imaging quality, and pain during injection. Recently, automated intra-arterial CO<sub>2</sub> injectors were developed. These new injectors overcome many constraints associated with injecting CO<sub>2</sub> in arteries during

revascularisation(7-11). This could lead to a shift in how arterial revascularisation is performed, preventing AKI and the major complications associated with it. Before this happens, the value of CO<sub>2</sub> via automated injectors as a means of preventing AKI post endovascular revascularisation needs to be tested in a randomised trial. We also need to understand the acceptability, feasibility and factors that may influence the adoption/implementation of the technology in the NHS, as per National Institute for Health and Care Research (NIHR) and Medical Research Council (MRC) guidance(12). This proposed randomised research will provide this necessary information to guide the implementation/adoption of this technology in the NHS, potentially leading to improved outcomes for patients and decreasing healthcare costs.

**Research questions:**

1. Does the use of CO<sub>2</sub> via an automated injector during endovascular revascularisation reduce: i) The likelihood of short and medium-term renal decline? ii) The volume of iodinated contrast medium necessary to complete the procedure?
2. What is the acceptability, feasibility and the factors that may influence the adoption of this technology in the NHS from the perspective of patients and practitioners?
3. What are the costs of performing endovascular lower limb revascularisation using an automated CO<sub>2</sub> injector, compared to the usual NHS standard of care (no use of CO<sub>2</sub>)?

**Objectives****Primary Objective:**

1. Perform a multicentre prospective randomised controlled trial (RCT) to assess whether using an automated CO<sub>2</sub> injector reduces the impact of endovascular

revascularisation on renal function in patients with PAD and CKD by reducing the amount of nephrotoxic iodinated contrast medium necessary to complete the revascularisation

### **Secondary Objectives:**

2. Assess the acceptability, feasibility and the factors that may influence the adoption of this technology in the NHS from the perspective of patients and practitioners
3. Record and report the overall costs of performing endovascular lower limb revascularisation using an automated CO<sub>2</sub> injector vs. the usual NHS standard of care.

## **METHODS AND ANALYSIS**

### **Trial Design**

Multicentre, prospective, open-label, parallel-group RCT. The trial will also include a health economic evaluation to assess cost-effectiveness from both an NHS and a wider English societal perspective.

### **Trial Setting**

Six NHS hospital sites in England providing arterial intervention services, which are already using the Angiodroid™ CO<sub>2</sub> injector. Pre-/post-operative care will follow local protocols of care (pragmatic RCT).

### **Inclusion criteria:**

- Age  $\geq 18$  years

- Undergoing any peripheral arterial revascularisation with an endovascular component
- Estimated glomerular filtration rate  $\leq 60 \text{ ml/min/1.73m}^2$  at baseline or known established chronic kidney disease (two separate eGFR readings  $< 60 \text{ ml/min/1.73m}^2$  in the last three months).
- Signed informed consent

**Exclusion criteria:**

- Known allergy to iodinated contrast media
- Individuals already on long-term dialysis at time of screening
- An inability to understand the languages in which the trial materials are provided.

***Inclusion criteria for healthcare professionals involved in the parallel non-randomised implementation study:***

Clinicians who have performed the revascularisation procedure for the patient participants included in the RCT.

**Interventions**

Participants will be randomised to either:

- **Control group:** Standard iodinated contrast medium used during endovascular PAD revascularisation (standard of care)
- **Intervention group:** CO<sub>2</sub> Contrast, delivered via a dedicated injector system (Angiodroid™ injector) as an alternative to iodine contrast.



All other procedural aspects remain consistent across groups and as per usual standard of care (pragmatic RCT). Those in the intervention group will be allowed the administration of standard iodine-based intra-arterial contrast if deemed necessary by the operators in order to complete the procedure safely.

## **Outcomes**

Outcomes and assessments are based on national and international consultation with AKI experts, our national stakeholder/patient survey, patients' opinions during our patient involvement work, and our previous/ongoing randomised and observational research relating to renal decline in vascular patients(1, 13).

We plan to evaluate the impact on kidney function post- endovascular revascularisation in the RCT arms both in the short term (AKI) and at 90 days (medium term). We will include creatinine measurements at 2, 30 and 90 days, powered to detect a clinically meaningful difference in SCr at 90 days. These three SCr measurements will also allow us to compare AKI incidence based on the Kidney Disease Improving Global Outcomes (KDIGO) definition of AKI between groups and calculate/compare incidence of major adverse kidney events at 90 days (MAKE outcome). This will provide novel information on the clinical value of using the proposed intervention, addressing the relevant evidence gap and leading to adoption of the intervention in the NHS, for the immediate benefit of patients in this high-risk group. We have chosen not to use AKI incidence at 2 days as the primary outcome as it does not allow us to evaluate medium-term renal injury and would also necessitate recruitment of a prohibitively large sample of patients, without adding clinical information that would aid translation to clinical care.

**Primary Outcome:**

Log serum creatinine measured from the blood sample taken at 2, 30 and 90 days (part of the standard of care) after endovascular revascularisation

**Secondary Outcomes:*****Key secondary outcome:***

Volume of iodinated contrast medium used during endovascular revascularisation.

The trial is adequately powered to assess both the primary outcome and the key secondary outcome. This will provide clinicians with high-quality definitive evidence and data necessary in order to adopt this intervention into their routine clinical practice.

***Other secondary outcomes:***

1. Proportion of participants developing AKI (per stage of AKI) within 2 days (48 hours) of procedure based on the Kidney Disease Improving Global Outcomes (KDIGO) definition of AKI-stages
2. Proportion of participants developing Major Adverse Kidney Events (MAKE) by 90-day follow-up. A MAKE event is defined as either death, new requirement for dialysis or worsening kidney function denoted by >25% decline in estimated Glomerular Filtration Rate (eGFR). Baseline eGFR will be defined as the most recent value before the procedure.
3. Time spent as an inpatient (days) since randomisation measured using patient medical records by a 90-day follow-up
4. Pain experienced during the procedure measured using a Visual Analogue Scale (VAS)
5. Quality of Life (QoL) at 90-day follow-up measured using the EQ-5D-5L and SF-36 questionnaires

6. The proportion of revascularisation completed as planned measured using patient medical records at one timepoint
7. Number of surgical or endovascular re-interventions measured using patient medical records by the 90-day follow-up
8. Perceived acceptability, feasibility and factors that may influence the adoption of CO<sub>2</sub> during each revascularisation by the practitioners/participants measured using the Theoretical Framework of Acceptability Questionnaire at the 90-day follow-up for patients, and post-procedure (administered within 3 days of the intervention) and cross-sectional questionnaires (administered after few months into recruitment) for practitioners.
9. Costs associated with each procedure (health economic analysis) measured using a Healthcare Resource Use questionnaire over a minimum 90-day period (end of clinical follow-up)

Fluid therapy and medical care per patient will be documented for both groups before and after the procedures, using a standardised data collection system, based on our completed NIHR-RfPB (Research for Patient Benefit) funded CHABLIS study(15, 16). Further, all equipment/devices used in each procedure will also be collected and the duration of the procedure will be documented, to allow an in-depth health-economic analysis (additional package funded separately).

### **Participant Timeline and Schedule of Events**

Participants will be screened and consented up to 15 days prior to the index procedure. Baseline assessments include medical history, demographics, height, weight, baseline

SCr, and patient-reported outcome measures relating to quality of life (using the patient-preferred EQ-5D-5L and SF-36 forms).

Randomisation occurs after consent and baseline measurements, allocating participants 1:1 to iodinated contrast medium or CO<sub>2</sub> via an automated injector. The index procedure (endovascular revascularisation) will be performed within 15 days of consent.

Follow-up assessments will coincide with routine NHS care at Days 2, 30, and 90 after the procedure. These include SCr measurements, repeat patient-reported outcome measures (Day 90), pain scores (Visual Analogue Scale [VAS] during the index procedure), and health care resource use questionnaires (Day 90).

An optional qualitative interview will be offered 3–4 weeks post-procedure to a purposive sample of participants and practitioners to explore intervention acceptability and implementation factors.

## **Statistical Considerations**

### **Sample Size Calculation**

174 patients (87 per group) provides 90% power to detect clinically meaningful differences. Based on our preliminary data (observational AKI study of 2,021 patients with PAD/CKD treated in three sites and a pilot study on the use of CO<sub>2</sub> in PAD procedures)(17, 18), we expect the standard deviation of log SCr values at 2, 30 and 90 days to be 0.25 log( $\mu\text{mol/L}$ ). We assume the correlation of the baseline, 2, 30, and 90-day measures to be 0.67, which is conservative. With these assumptions, a sample size of 156 patients (78 per group) would have a 90% power to detect a mean difference of 0.075 log( $\mu\text{mol/L}$ ) in SCr values (effect size of 0.3) at 2, 30, and 90-days post-surgery, between

intervention and control groups with an alpha value of 0.05. Allowing for 10% drop out, 174 will be recruited. This sample size will also allow us to assess for a 20% reduction in the volume of iodinated contrast used in those having the intervention vs. control (median of 70ml of iodinated contrast used in our published series without CO<sub>2</sub>). In order to ensure the population remained truly per intention to treat (ITT) for the primary outcome, multiple imputation will be implemented to deal with missing data in instances where participants are missing any of the SCr values. Values will be predicted using a multivariate normal regression equation with 20 imputations being used.

## **Recruitment**

Potential participants will be identified during routine clinical care in NHS vascular clinics and multidisciplinary team meetings at participating sites. Patients scheduled for endovascular revascularisation who meet the inclusion criteria will be approached by local clinical teams. Eligible patients will be provided with verbal and written information about the trial and given sufficient time to consider participation.

Written informed consent will be obtained by trained research staff prior to any trial-specific procedures. Recruitment will be supported by site investigators, research nurses, and the wider clinical team. PPI&E representatives have reviewed all participant-facing materials to ensure clarity and acceptability. Recruitment will be monitored by the coordinating team, with regular feedback provided to sites to maintain recruitment targets across all participating NHS Trusts.

Participating NHS organisations/Trust (recruiting sites):

University Hospitals of Leicester NHS Trust

Manchester University NHS Foundation Trust St George's NHS Trust

Hull University Teaching Hospitals NHS Trust

University Hospitals of North Midlands

St George's University Hospitals NHS Foundation Trust

Royal Free London NHS Foundation Trust

### **Assignment of Interventions and Randomisation**

1:1 electronic randomisation. Minimisation based on CKD stage, age, diabetes, and tissue loss.

### **Data Collection, Management and Analysis**

#### **Data Collection Methods**

Clinical and patient-reported data will be collected by trained research staff at each participating NHS site, supported by the coordinating Clinical Trials Unit (CTU). Data will be collected at baseline, during the index procedure, and at follow-up visits at Days 2, 30, and 90, which coincide with routine NHS care.

Baseline data will include demographics, medical history, comorbidities, height, weight, and baseline SCr. Procedural data will include details of the intervention, type and volume of contrast used, pain scores using a VAS, and any immediate complications.

Follow-up data will include repeat SCr measurements, assessment of adverse events (AEs), MAKE, re-interventions, hospital stay duration, and patient-reported outcome measures (EQ-5D-5L and SF-36) at Day 90. Healthcare resource use will be captured via

case report forms (CRFs) and participant questionnaires to inform the health economic evaluation.

Optional qualitative data will be collected via semi-structured interviews with a purposive sample of participants and practitioners to explore acceptability, feasibility, and implementation factors. Interviews will be conducted by trained qualitative researchers following a topic guide.

All data will be entered into a secure, validated electronic data capture system managed by the CTU. Source data verification and monitoring will be conducted according to the trial monitoring plan and Sponsor standard operating procedures (SOPs).

### **Data Management and Monitoring**

- Data will be collected via appropriate approved electronic CRFs and software (secure and encrypted) and managed by Leicester Clinical Trials Unit (LCTU).
- An independent Data Monitoring Committee (DMC) will oversee the trial.
- Serious adverse events will be reported per NHS established Good Clinical Practice (GCP) guidelines.
- Monitoring as per Sponsor SOPs.

### **Trial Management**

The KID Trial will be managed by the Leicester Clinical Trials Unit (LCTU), a UK Clinical Research Collaboration (UKCRC)-registered Clinical Trials Unit (registration number 43), co-located with the Chief Investigator (CI) at the University of Leicester (UoL). The LCTU will provide trial management, statistical, data, and quality oversight

support throughout the trial duration. The study is sponsored by the University of Leicester (contact: [rgosponsor@le.ac.uk](mailto:rgosponsor@le.ac.uk)).

Trial oversight will be provided through three key governance structures: the Trial Management Group (TMG), the Trial Steering Committee (TSC), Data Monitoring Committee (DMC). The TMG will meet weekly or needed, and will be responsible for the day-to-day operational management of the trial. It will include the CI, co-applicants, the trial manager, the lead statistician, and two lay co-applicants. The lay co-applicants will also liaise with an independent lay advisory group to ensure patient-centered conduct and delivery of the trial. The TSC will meet at least every six months. It will be chaired by an independent member and include external clinical, statistical, and lay representatives. The TSC will provide high-level oversight, ensure adherence to the protocol, and advise on trial progress and conduct.

The DMC will meet separately, prior to each TSC meeting. Comprising independent clinical and statistical experts, including an independent Chair, the DMC will review accumulating trial data with respect to participant safety and data integrity. It will make recommendations to the TSC regarding the continuation, modification, or termination of the trial based on these reviews.

### **Data Analysis**

The LCTU Trial Statistician will be responsible for planning, monitoring and carrying out analyses, supervised by a senior statistician. Statistical analysis will be undertaken according to a pre-specified statistical analysis plan (SAP) written prior to database lock and reported following Consolidated Standards of Reporting Trials (CONSORT)



statements. The baseline characteristics of the participants will be summarised by group. Continuous variables will be summarised using mean and standard deviation, or median and inter-quartile range if data do not have a symmetric distribution. Categorical variables will be summarised with counts and percentages. The primary analysis of the primary outcome will be carried out in the ITT population using a mixed effects model with participant as random effect to account for repeated measures over time. Each participant will contribute up to 3 repeated outcome measures to the model in addition to the baseline SCr. The model will be adjusted for the stratification and minimisation variables (age, sex, baseline CKD stage, presence of tissue loss). Secondary outcomes will be analysed on a complete case population and reported similarly to the primary outcome using appropriate methodology to compare randomised groups; binary outcomes using logistic regression, continuous outcomes using linear regression or where not normally distributed using appropriate non-parametric methods.

### **Implementation and Process Evaluation**

A mixed-methods explanatory design will explore the acceptability, feasibility, and factors influencing implementation. The evaluation is informed by Proctor et al.'s Implementation Outcome Framework, the Theoretical Framework of Acceptability (TFA).

**Patient participants:** All trial participants will complete the 8-item TFA questionnaire at each assessment time point. Up to 12 participants will be purposively sampled for qualitative interviews 3–4 weeks post-procedure, conducted face-to-face or remotely by an experienced researcher using a semi-structured, iterative guide co-developed with PPI&E representatives.

**Practitioner participants:** All practitioners performing the procedures will complete online surveys (TFA, Intervention Appropriateness, Feasibility of Intervention Measure, Innovation-Specific Implementation Intentions) within 72 hours post-procedure. Up to 20 practitioners will be purposively sampled for qualitative interviews exploring training, delivery, and implementation barriers/facilitators. Interviews will be transcribed and analysed thematically using TFA domains, with participant checking and PPI&E/advisory input to contextualise findings.

### **Health Economic Evaluation**

A micro-costing analysis will capture intraprocedural costs, including devices, consumables, and staff time. Additional NHS and community health service use will be collected over 90 days, alongside EQ-5D-5L for QALY estimation. Secondary analyses will include productivity losses. Where appropriate, long-term outcomes will be modelled using a state-transition approach. Sensitivity analyses will assess uncertainty. All analyses will follow National Institute for Health and Care Excellence (NICE) and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines.

### **Measurement of Costs and Outcomes**

Health economic analysis includes direct and indirect costs.

### **Statistical Methods**

#### **Planned Analyses for Primary and Secondary Outcomes**

The primary analysis will be performed on an ITT basis, including all randomised participants as allocated. The primary outcome — log serum creatinine (SCr) at 2, 30,

and 90 days post-procedure — will be analysed using a mixed-effects model with participant as a random effect to account for repeated measures over time. The model will adjust for baseline log SCr, stratification and minimisation factors (age, sex, baseline CKD stage, and presence of tissue loss).

Secondary outcomes will be analysed using appropriate statistical methods: binary outcomes (e.g., AKI incidence, MAKE) will be compared between groups using logistic regression; continuous outcomes (e.g., contrast volume, quality of life scores) will be analysed using linear regression, or non-parametric tests if data are not normally distributed. Time-to-event data, if applicable, will be analysed using survival analysis methods such as Kaplan–Meier estimates and Cox proportional hazards regression. All analyses will be conducted using validated statistical software according to a pre-specified SAP.

### **Handling of Missing Data**

Missing outcome data will be assessed for extent and patterns. For the primary outcome, multiple imputation using a multivariate normal regression model will be applied if data are missing at random, with results pooled across imputed datasets. Sensitivity analyses will be conducted to evaluate the impact of different assumptions about missing data. Secondary outcomes will be analysed on a complete case basis, unless otherwise specified.

### **Ethics and Dissemination**

The trial has received full ethical approval from an NHS Research Ethics Committee [REC reference: 24/WA/0332; contact: [wales.rec7@wales.nhs.uk](mailto:wales.rec7@wales.nhs.uk)]. All amendments,

including NSA01 (clarifying protocol deviations, randomisation/recruitment timelines, introduction of the compiled questionnaire booklet, and secure interview transcription method) and NSA02 (clarifying inclusion criteria for CKD participants), have been reviewed and approved to ensure continued compliance with regulatory requirements.

Written informed consent will be obtained from all participants before any trial-specific procedures take place. Consent will include agreement for participation in the main trial and any optional qualitative sub-study components. Participant Information Sheets (PIS) and Informed Consent Forms (ICF) have been updated to reflect changes described in the approved amendments, including the use of secure, encrypted transcription devices for interviews and the introduction of the compiled questionnaire booklet. All participant information will be kept strictly confidential and handled in line with the General Data Protection Regulation (GDPR) and UK Data Protection Act. Personal identifiers will be stored securely at sites and not transferred to the trial database. Audio recordings of interviews will be encrypted and securely transcribed using a standalone device to prevent unauthorised access. Practitioner identifiers have been updated in line with data protection best practice.

Trial results will be disseminated through publication in peer-reviewed journals and presentations at national and international conferences (e.g., American Vascular Society conference, European Society for Vascular Surgery conference). Lay summaries and updates will be shared through lay collaborators, community networks, and social media channels. A hybrid event for patients and the public will be organised to present key findings, supported by accessible outputs such as infographics, video summaries, and a dedicated trial webpage hosted by Vascular Research UK.

## **Access to Data**

Access to the final trial dataset will be limited to authorised trial team members only; however, anonymous data will be shared based on Health Research Authority guidance with scientific collaborators who can/will contact the study investigators. Any data sharing will be in anonymised form and compliant with participant consent and applicable data protection legislation.

## **Patient and Public Involvement and Engagement (PPI&E) before and during trial delivery**

PPI&E representatives are involved with design, delivery, and dissemination strategies. Three lay focus groups have been convened to develop this trial. Ten patients who had endovascular PAD treatment previously, two full-time carers, and two partners took part. We explored outcomes of interest, follow-up procedures, and clinically important differences. We gave participants multiple options to choose from regarding all of the above. We also asked them to volunteer their own views/opinions both in open discussions and individual face-to-face interviews. Two formal PPI&E co-applicants, a female and male patient (different ethnic backgrounds) who have had PAD procedures, support this trial. They will join all trial meetings, review trial-materials, and support dissemination. The two PPI&E co-applicants will lead the final dissemination event which we will host upon completion of the trial to share findings with patient networks and NHS staff nationally.

## **DISCUSSION**

The KID trial addresses a critical and currently unmet need in the management of patients with peripheral arterial disease (PAD) and chronic kidney disease (CKD) undergoing endovascular intervention(1). Acute kidney injury (AKI) is a common and serious complication in this population, largely attributed to the use of iodinated contrast medium. This multicentre, randomised controlled trial will evaluate whether the use of carbon dioxide (CO<sub>2</sub>) delivered via an automated injector (Angiodroid™) can reduce the incidence and severity of renal impairment in the short and medium term, compared with standard iodinated contrast.

While previous observational studies have indicated a potential benefit of CO<sub>2</sub> angiography in preserving renal function, this will be the first trial to evaluate its use systematically in a PAD/CKD cohort using robust clinical, implementation, and health economic endpoints. Incorporating a mixed-methods process evaluation and qualitative analysis ensures that acceptability, feasibility, and implementation barriers are explored in both patients and practitioners.

Several practical and operational challenges are anticipated. These include variation in operator experience with CO<sub>2</sub> delivery, ensuring high-quality imaging, and managing procedural discomfort which some patients may experience. Further, CO<sub>2</sub> injectors are not yet widely used across all NHS centres, requiring site-specific support and training. Patient follow-up at three separate timepoints (2, 30, and 90 days) also presents logistical demands, particularly in a population that may have mobility or access issues.

Nonetheless, the trial is strengthened by its pragmatic design, national recruitment strategy, and the use of existing NIHR infrastructure. A data management plan and engagement with experienced vascular centres will help ensure consistency in intervention delivery and data collection. The trial has been co-developed with extensive patient and public involvement (PPI&E), ensuring relevance of outcomes and acceptability of follow-up protocols.

If successful, the KID trial could support a shift in clinical practice by providing definitive evidence on the utility of automated CO<sub>2</sub> angiography in reducing AKI, potentially influencing NICE guidelines and NHS resource allocation. A reduction in AKI incidence could not only improve clinical outcomes, but also yield substantial cost savings for the healthcare system. The findings will therefore have significant implications for both clinical and policy decision-making in vascular care.

## **AUTHORS' CONTRIBUTIONS**

AS is the Chief Investigator; he conceived the trial and led the protocol development. NR, PC, AD, LB, NS, CB, SB, CR, HG, DA, and RS contributed to trial design. DA and KH provided patient and public involvement and engagement input. All authors read and approved the final manuscript and have been involved in producing the manuscript.

## **FUNDING STATEMENT**

This trial is funded by the National Institute for Health and Care Research, Reference: NIHR206198. The funder had no role in the trial design, data collection, analysis, interpretation, or in writing the manuscript.

## **COMPETING INTERESTS STATEMENT**

This protocol document and manuscript adheres to the Standard Protocol Items:

Recommendations for Interventional Trials (SPIRIT) guidance. Authors and collaborators have no conflicts of interest to declare. AS and AD are funded by the NIHR (no competing interest).

## **TRIAL STATUS AND DOCUMENTS**

Protocol version: 1.2 (2nd June 2025)

Trial registration: IRAS ID: 340062; ISRCTN registration: 23564393

Funder's reference number: NIHR206198

Ethical approval: 24/WA/0332

Recruitment start date: 01 December 2024

Expected recruitment completion: 31 December 2025

## **REFERENCES**

1. Katsogridakis E, Lea T, Yap T, Batchelder A, Saha P, Diamantopoulos A, et al. Acute kidney injury following endovascular intervention for peripheral artery disease. *Br J Surg.* 2021;108(2):152–9.
2. Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, et al. Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia. *Eur J Vasc Endovasc Surg.* 2019;58(1S):S1–S109.e33.
3. Burckenmeyer F, Schmidt A, Diamantis I, Lehmann T, Malouhi A, Franiel T, et al. Image quality and safety of automated carbon dioxide digital subtraction angiography in femoropopliteal lesions: Results from a randomized single-center study. *Eur J Radiol.*



2021;135:109476.

4. Luders F, Malyar N, Meyborg M, Gebauer K, Brand E, Reinecke H. Impact of peripheral arterial occlusive disease on the development of contrast medium-induced acute kidney injury. *Nephron Clin Pract.* 2012;122(1–2):38–43.
5. Pistolesi V, Regolisti G, Morabito S, Gandolfini I, Corrado S, Piotti G, et al. Contrast medium induced acute kidney injury: a narrative review. *J Nephrol.* 2018;31(6):797–812.
6. Katsogridakis E, Saha P, Diamantopoulos A, Saratzis N, Davies R, Zayed H, et al. Long-Term Effects of Acute Kidney Injury Following Endovascular Femoropopliteal Intervention: Insights From a Multicenter Trial. *J Endovasc Ther.* 2022:15266028221136436.
7. Massaini G, Lazzarotto T, Masciello F, Panci S, Michelagnoli S, Chisci E. A Pilot Study of Endovascular Repair for Ruptured Aortic Aneurysms With the Use of Carbon Dioxide Angiography Alone. *J Endovasc Ther.* 2023:15266028231180995.
8. Vacirca A, Faggioli G, Mascoli C, Gallitto E, Pini R, Spath P, et al. CO<sub>2</sub> Automated Angiography in Endovascular Aortic Repair Preserves Renal Function to a Greater Extent Compared with Iodinated Contrast Medium. *Ann Vasc Surg.* 2022;81:79–88.
9. Thomas RP, Viniol S, Konig AM, Portig I, Swaid Z, Mahnken AH. Feasibility and safety of automated CO<sub>2</sub> angiography in peripheral arterial interventions. *Medicine (Baltimore).* 2021;100(2):e24254.
10. Ghumman SS, Weinerman J, Khan A, Cheema MS, Garcia M, Levin D, et al. Contrast induced-acute kidney injury following peripheral angiography with carbon dioxide versus iodinated contrast media: A meta-analysis and systematic review of current literature. *Catheter Cardiovasc Interv.* 2017;90(3):437–48.

11. Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. *BMJ*. 2021;374:n2061.
12. Billings FTt, Shaw AD. Clinical trial endpoints in acute kidney injury. *Nephron Clin Pract*. 2014;127(1–4):89–93.