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FULL/LONG TITLE OF THE STUDY

LO-PAIgN: Mediators of Loin Pain in IgA Nephropathy

SHORT STUDY TITLE / ACRONYM

LO-PAIgN

PROTOCOL VERSION NUMBER AND DATE

- V2.0_21/05/2026

IRAS number:	364280
Sponsor:	University of Leicester
Sponsor number:	1104
Funder(s) number:	Not Applicable
Study registration number:	Not Applicable

This protocol has regard for the HRA guidance and the University of Leicester Sponsor Standard Operating Procedures (SOPs)

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, the UK Policy Framework for Health and Social Care Research, and other relevant regulatory requirements.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the study without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given. Any discrepancies and serious breaches of GCP from the study as planned in this protocol will be explained.

The below table should be completed after regulatory approval has been obtained.

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Name: (please print):	Dr Haresh Selvaskandan
Signature:	x
Date:	x
Principal Investigator:	
Site:	University of Leicester
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Signature:	x
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NIHR Portfolio adopted	No

ROLE OF THE STUDY SPONSOR

The Sponsor for this research project is the University of Leicester.

The University of Leicester is responsible for the design, management and outputs of the research. Participating research sites are responsible for the conduct of the study within their organisation.

The Research Governance Office review and approve all iterations of the protocol as part of the Sponsor review and amendment review processes. Further information is available from the Sponsor Standard Operating Procedures webpage.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

Not Applicable

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STUDY SUMMARY

Short Study Title or Acronym	Mediators of Loin Pain in IgAN	
Study Design	Observational Study	
Study Participants	IgA Nephropathy (IgAN) patients with intermittent/episodic loin pain IgA Nephropathy (IgAN) patients with no history of loin pain	
Sample Size	Total Participants: 40 20 IgAN patients with intermittent loin pain 20 IgAN patients with no history of loin pain Total Samples: 60 Patients with intermittent loin pain give samples twice: 1) During an active pain flare (~20 samples); 2) No active pain flare (~20 samples) Patients with no history of loin pain only give samples once (~20 samples)	
Follow up duration	No Follow-up as it is an observational study	
Planned Study Period	22/09/2025-21/09/2028	
	Objectives	**End Points / Outcome Measures**
Primary	Specialised renal MRI scans will be performed (T1-weighted imaging and T1 and T2 mapping) on the patient groups. To assess the presence of any collecting system changes, T1-weighted images of the renal pelvis will also be taken.	To identify structural and functional differences in the kidneys between patients with active loin pain, no active pain, and no history of loin pain. Downstream collecting system changes will be recorded and accounted for in the analysis. **Outcome Measures:** Differences in total kidney volume, renal cortical and medullary volume, renal oedema, and probable involvement of downstream collecting system changes in loin pain.

Secondary	1) Untargeted Liquid Chromatography-Tandem Mass spectrometry (LC-MS/MS) analysis will be performed on patient urine samples to see different biologically relevant molecules present in urine. 2) Additional molecules of interest in blood and urine will be measured via ELISA and Luminex assays. 3) Perform the urine dipstick test and compare the presence of cells in urine using microscopy between patient groups 4) Exploratory: Compare the Kidney function lab test results accessed from patient records within Cohort A to identify any links between loin pain and kidney function	1) LC-MS/MS will provide a summary of biological molecules present in urine, which will then be used to identify active biological processes, such as pain signalling and inflammation during a loin pain flare, compared to those without pain. **Outcome Measures:** Differences in area under curve values, abundance ratios, and absolute concentrations. 2) This analysis will validate LC-MS/MS findings and quantify other mediators that could be involved in relevant processes like inflammation and nociception (pain signalling). The comparison between patient groups will help to determine whether the expression of specific mediators increases during an active pain flare, offering insight into the underlying mechanisms. **Outcome Measures:** Differences in weight/volume or volume/volume concentration and optical density between groups.

		3) The urine dipstick test would detect the presence of various factors like haematuria, proteinuria and infections. Microscopy would reveal the presence of RBCs, white blood cells (WBCs), and RBC, and granular casts in each patient group, giving clues about active kidney injury **Outcome Measures:** Difference in presence (Qualitative), cell count per high magnification field 4) Comparing kidney function tests, including eGFR, urea, proteinuria, etc., would help assess if loin pain is linked to kidney function. **Outcome Measures**: Differences in kidney function factors like eGFR, urea, minerals, proteinuria, etc.

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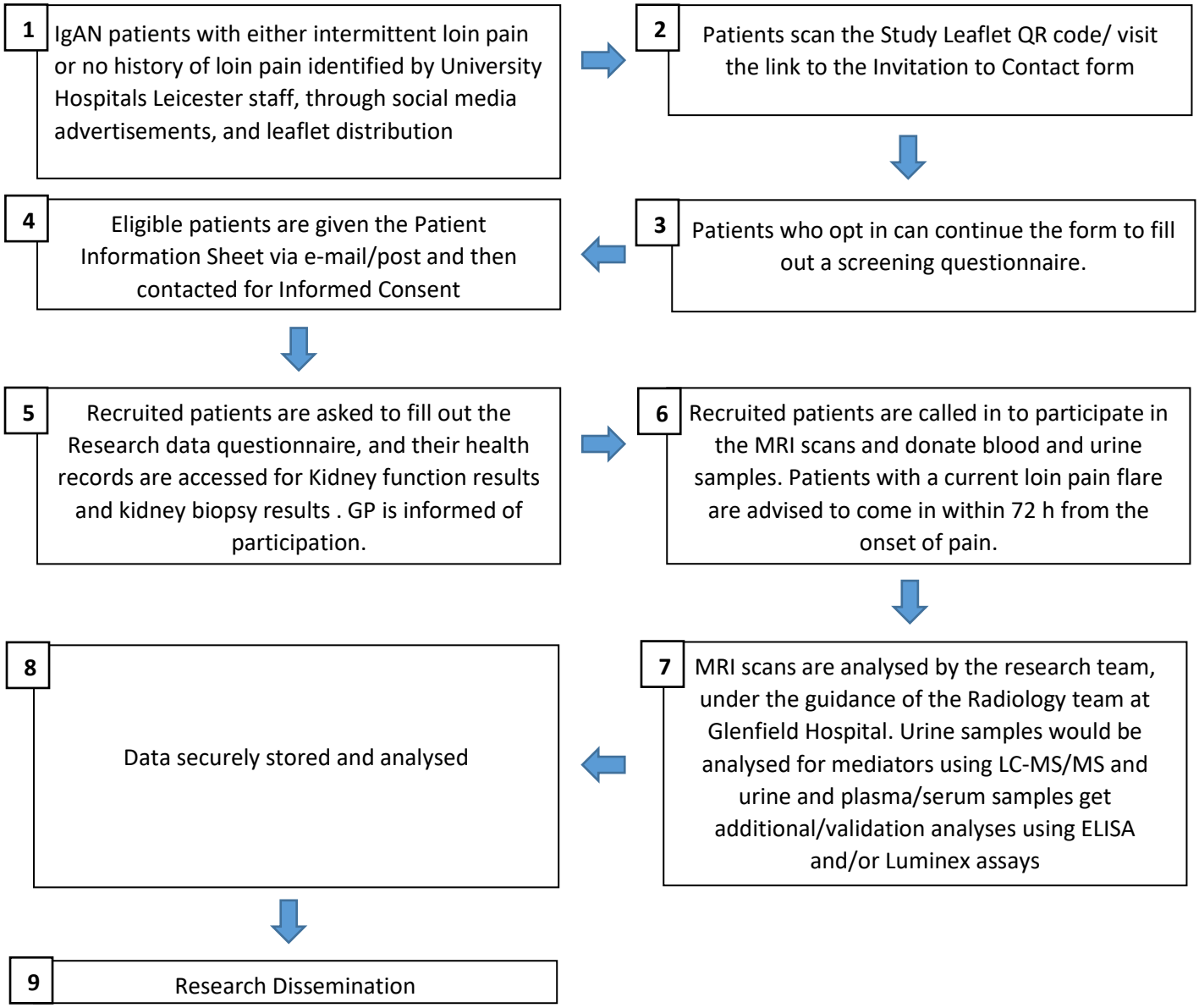
STUDY FLOW CHART



LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
ICF	Informed Consent Form
ISF	Investigator Site File
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIS	Participant Information Sheet
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure

KEY WORDS

IgAN: Immunoglobulin A Nephropathy

eGFR: Estimated Glomerular Filtration Rate

IoC: Invitation to Contact

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PROTOCOL AMENDMENT HISTORY

Amendment Reference	Protocol version no.	Protocol Date	Author(s) of changes	Summary of changes made

2 Background and Rationale

Glomeruli are microscopic structures in the kidneys which filter blood. Immunoglobulin A nephropathy (IgAN) is the most common primary glomerular disease reported worldwide. IgAN leads to a gradual loss of kidney function and has a high risk of progression to complete kidney failure over time. (1) It is often diagnosed among young adults. (1) IgAN presents with a host of clinical signs, including haematuria (blood in urine), proteinuria (protein in urine) and kidney function decline (measured using estimated glomerular filtration rate or eGFR). (2) According to a recent research survey conducted by our lab, 71% of respondents with IgAN report a lesser-known symptom of IgAN, i.e., episodic, mild to moderate, aching kidney/loin pain. (3) Similarly, in a recent social media survey, patients with IgAN described loin pain to be unrelenting and intrusive and suggested that healthcare professionals often dismissed their symptoms either due to a lack of knowledge or good treatments. (4)

Loin pain has also been reported in acute kidney injury due to IgAN in a case study, and in other chronic kidney diseases, such as thin glomerular basement membrane disease (thin GBM) and autosomal dominant polycystic kidney disease (ADPKD). (5-7) It has been speculated that a condition called Loin Pain Haematuria Syndrome (LPHS) may occur in glomerular disease, with documented LPHS in IgAN and thin GBM disease. This condition involves the simultaneous occurrence of loin pain and haematuria. (8, 9) In the context of thin GBM disease, a small-scale study observed that 40% of the renal tubules (tubes that carry filtrate or waste fluid filtered out from the blood) were completely filled with Red Blood Cells (RBCs) as seen in the kidney biopsy tissue samples. (10) This study also observed a relationship between the onset of haematuria and the onset of loin pain, suggesting a link between both in thin GBM disease. (10) The mechanisms for this are not well understood, but it has been proposed that it could be due to the obstruction of multiple renal tubules with RBCs, causing backflow of the filtrate, leading to kidney volume expansion and loin pain. (10) Furthermore, bilateral (both sides of the abdomen) loin pain is associated with severe glomerulonephritis (immune-cell influx and resulting injury) that often presents with oedema (swelling) and, in some cases, obstruction of multiple renal tubules with RBCs. (7, 11-14) This supports the findings of the small-scale study on thin GBM discussed above, and suggests that other similar glomerular diseases, such as IgAN, which is often associated with blood in the urine, could similarly present with loin pain. Although this study was performed three decades ago, few attempts have been made to investigate this until now. Since then, there have been multiple small-scale observational studies and case reports that point towards the same link between loin pain and haematuria in IgAN. (7, 11-15) However, the mechanism and cause of nociception (pain signalling) are unclear in IgAN. From self-reported surveys, it is clear that loin pain has adverse psychosocial impacts on patients' lives, highlighting the need for further investigation and management. (3)

IgAN is an immune-mediated disease that leads to kidney inflammation as a result of Galactose-deficient IgA (Gd-IgA)-containing immune complexes depositing within the kidneys. Therefore, the role of inflammation (influx of immune cells) may be

important in loin pain signalling.(2) IgAN is accompanied by activation of complement (a part of the immune system), immune-cell infiltration, release of pro-inflammatory cytokines and chemokines (proteins that promote inflammation), and mesangial cell (a subset of kidney cells) activation and proliferation. Some of these pro-inflammatory cytokines, such as Tumour Necrosis Factor-alpha (TNF-α) and Interleukin 1-beta (IL-1β), can sensitise renal nerves for pain signalling known as nociceptors. (16) The renal environment in IgAN is highly immunogenic (ability to produce an immune response); hence, it is reasonable to hypothesise that inflammatory cytokines and complement proteins may play a role in loin pain. This study will examine the expression of these proteins, as renal inflammation has been shown to alter the sensitivity of nociceptors and promote cytokine-mediated pain hypersensitivity (where small triggers cause a stronger pain signal than normal). (17-19)

A recent survey conducted by our research group found that the prevalence or severity of loin pain in patients with IgAN may not be related to their eGFR (a standard measure of kidney function). This suggests that patients with IgAN may present with loin pain even without advanced kidney disease. We therefore also aim to investigate whether molecules known to contribute to peripheral or central sensitisation of nociceptors may be contributing to loin pain in IgAN. Peripheral sensitisation refers to the reduction in the pain threshold of nociceptors (making them more responsive to stimuli). (20) Over time, this can develop into central sensitisation, where neurons in the spinal cord dorsal horn become hyperexcitable, leading to chronic pain. (21) A wide range of signalling molecules have been implicated in peripheral sensitisation, including protons, ATP, prostaglandins, thromboxanes, leukotrienes, nerve growth factor (NGF), granulocyte-macrophage colony-stimulating factors (G-CSF, GM-CSF), cytokines (TNF-α, IL-1β, IL-6), chemokines, neurotransmitters (bradykinin, substance P, calcitonin gene-related peptide -CGRP, and histamine), lipids, etc. (20) Measuring the levels of these molecules may indicate activation of pathways known to drive peripheral sensitisation, particularly if loin pain cannot be explained by kidney damage. This analysis will therefore form part of the urine/serum evaluation phase of our study.

This study will be the first to investigate the mediators of loin pain in IgAN, as there is currently little published knowledge available on this topic. No mechanisms have been definitively shown as a cause of loin pain; however, kidney pathology, immune processes, and alterations in pain signalling are thought to be involved. Therefore, we hypothesise that loin pain in IgAN patients is driven by three possible mechanisms: 1) structural kidney pathology, including capsular stretch (increased kidney volume/size), and oedema/inflammation/fibrosis; 2) immune-mediated damage and pain signalling; 3) pathways that can lead to peripheral or central sensitisation. To investigate these mechanisms, we will divide patients with IgAN into 2 cohorts: Cohort A- patients who experience intermittent loin pain (loin pain in episodes), and Cohort B- patients with no history of loin pain. Cohort A would be further divided into two sample collection timepoints: 1) During an active pain flare (within 72 h of onset); 2) No active pain (control). The following objectives will be used to assess the differences:

1) Specialised renal MRI scans will be performed (T1-weighted imaging and T1 and T2 mapping) on the patient groups. To assess the presence of any collecting system changes, T1-weighted images of the renal pelvis will also be taken.

2) Untargeted Liquid Chromatography-Tandem Mass spectrometry (LC-MS/MS) analysis will be performed on patient urine samples to see different biologically relevant molecules present in urine.

3) Additional molecules of interest in blood and urine will be measured via ELISA and Luminex assays.

4) Perform the urine dipstick test and compare the presence of cells in urine using microscopy between patient groups

5) Exploratory: Compare the Kidney function lab test results accessed from patient records within Cohort A to identify any links between loin pain and kidney function

Through this study, we should be able to pinpoint which underlying mechanisms are most likely causing loin pain in IgAN patients, helping advance the knowledge of this poorly understood, debilitating condition. Our study could also help to shed light on loin pain in other similar glomerular diseases like thin GBM, benefiting a wider group of patients. It would also pave the way for more comprehensive studies with a larger sample size, making way towards targeted therapy.

3 Objectives and Outcome Measures/Endpoints

Objectives	Outcome Measures/Endpoints	Timepoint(s) of evaluation of this outcome measure
Primary Objective, Outcome, Timepoint(s)		

Specialised renal MRI scans will be performed (T1-weighted imaging and T1 and T2 mapping) on the patient groups. To assess the presence of any collecting system changes, T1-weighted images of the renal pelvis will also be taken.	To identify structural and functional differences in the kidneys between patients with active loin pain, no active pain, and no history of loin pain. Downstream collecting system changes will be recorded and accounted for in the analysis. **Outcome Measures:** Differences in total kidney volume, renal cortical and medullary volume, renal oedema, and probable involvement of downstream collecting system changes in loin pain.	**Cohort A: IgAN patients with intermittent loin pain** Timepoint 1: Within 72 hours of loin pain onset Timepoint 2: No active loin pain **Cohort B: IgAN patients with no loin pain** Timepoint: No specific requirement
Secondary Objective(s), Outcome(s), Timepoint(s)		
Untargeted Liquid Chromatography-Tandem Mass spectrometry (LC-MS/MS) analysis will be performed on patient urine samples to see different biologically relevant molecules present in urine.	LC-MS/MS will provide a summary of biological molecules present in urine, which will then be used to identify active biological processes, such as pain signalling and inflammation during a loin pain flare, compared to those without pain. **Outcome Measures:** Differences in area under curve values, abundance ratios, and absolute concentrations.	**Cohort A: IgAN patients with intermittent loin pain** Timepoint 1: Within 72 hours of loin pain onset Timepoint 2: No active loin pain **Cohort B: IgAN patients with no loin pain** Timepoint: No specific requirement
Additional molecules of interest in blood and urine will be measured via ELISA and Luminex assays.	ELISA/Luminex assays will validate LC-MS/MS findings and quantify other mediators that could be involved in relevant processes like inflammation and nociception (pain signalling). The comparison between patient groups will help to determine whether the expression of specific mediators increases during an active pain flare, offering	**Cohort A: IgAN patients with intermittent loin pain** Timepoint 1: Within 72 hours of loin pain onset Timepoint 2: No active loin pain **Cohort B: IgAN patients with no loin pain**

	insight into the underlying mechanisms. **Outcome Measures:** Differences in weight/volume or volume/volume concentration and optical density between groups.	Timepoint: No specific requirement
Perform urine dipstick test and compare the presence of cells in urine using microscopy between patient groups	The urine dipstick test would detect the presence of various factors like haematuria, proteinuria, glucose, etc. Microscopy would reveal the presence of RBCs, White Blood Cells (WBCs), and RBC and Granular casts in each patient group, giving clues about active kidney injury **Outcome Measures:** Difference in Presence (Qualitative), cell count per high magnification field	**Cohort A: IgAN patients with intermittent loin pain** Timepoint 1: Within 72 hours of loin pain onset Timepoint 2: No active loin pain **Cohort B: IgAN patients with no loin pain** Timepoint: No specific requirement
Tertiary/Exploratory Objective(s), Outcome(s), Timepoint(s)		
Compare the Kidney function lab test results accessed from patient records within Cohort A to identify any links between loin pain and kidney function	Comparing kidney function lab test factors like eGFR, urea, proteinuria, minerals, etc., would help assess if loin pain is linked to kidney function. **Outcome Measures**: Difference in kidney function Differences in kidney function factors like eGFR, urea, minerals, proteinuria, etc.	**Cohort A: IgAN patients with intermittent loin pain** Timepoint 1: Within 72 hours of loin pain onset Timepoint 2: No active loin pain

4 Study Design

This is a multi-centre study, involving University Hospitals Leicester (Glenfield Hospital and Leicester General Hospital) and the University of Leicester. It is a cross-sectional and longitudinal observational study, wherein patients would be invited to Glenfield Hospital for MRI scans and blood & urine collection. Leicester General Hospital would

only be used for patient recruitment, including identifying participants by their direct healthcare teams.

5 Participant Eligibility Criteria

Cohort A (IgAN patients with intermittent loin pain) would act as their own controls as samples and scans would be taken once during an active flare and other when they are not currently experiencing pain. Cohort B (IgAN patients with no history of loin pain) acts as a control group for how the parameters of an IgAN patient without loin pain would look.

5.1 Inclusion criteria

Cohort A

1) ≥18 years of age at the time of recruitment
2) IgAN diagnosis confirmed with a renal biopsy
3) Episodic/Intermittent Loin Pain (defined as pain at least once every 6 months)
4) Have the capacity to consent to the study

Cohort B

1) ≥18 years of age at the time of recruitment
2) IgAN diagnosis confirmed with a renal biopsy
3) No history of loin pain
4) Have the capacity to consent to the study

5.2 Exclusion criteria

Cohort A

1) Constant loin pain
2) Infrequent loin pain (no pain experienced in the last 6 months)
3) Inability to differentiate loin pain from back pain
4) Other renal diseases
5) Therapies that interfere with immune-mediation like steroids and complement inhibitors
6) Kidney transplant recipients
7) Current participation in an interventional study that may affect kidney function
8) Patients on dialysis
9) Patients with implants that are not MRI-safe (pacemakers, implantable defibrillators, cochlear implants, some shunts, neurostimulators, some aneurysm clips, etc.)

Cohort B

1) Other renal diseases
2) Therapies that interfere with immune-mediation like steroids and complement inhibitors
3) Kidney transplant recipients
4) Current participation in an interventional study that may affect kidney function
5) Patients on dialysis
6) Patients with conditions/implants that are not MRI-compatible (claustrophobia, pacemakers, implantable defibrillators, cochlear implants, some shunts, neurostimulators, some aneurysm clips, etc.)

6 Study Schedule

6.1 Schedule of procedures

Cohort A:

Procedures			Visits			
	Pre-screening	Screening	Consent	After Consent		
Visit window			± X days/weeks			
Visit details	Remote OR during Routine Visit	Remote	Face-to-face OR remote	Remote	Study Visit 1 (within 72 hours of loin pain)	Study visit 2 (No active pain)
Handing out Study Leaflet	x					
Invitation to Contact Form	x					
Eligibility Assessment		x				
Informed consent			x			
Symptom Assessment					x	
Blood Pressure reading					x	x
MRI scan					x	x
Blood/Urine Collection					x	x
Research Data Questionnaire				x		
Medical history		x		x		
Contacting GP/healthcare team				x		
Accessing Medical Records				x		

Cohort B:

Procedures			Visits		
	Pre-screening	Screening	Consent	After Consent	
Visit window			± X days/weeks		
Visit details	Remote OR during Routine Visit	Remote	Face-to-face OR remote	Remote	Study Visit
Handing out Study Leaflet	x				
Invitation to Contact Form	x				
Eligibility Assessment		x			
Informed consent			x		
Pain Assessment					
Blood Pressure reading					x
MRI scan					x
Blood/Urine Collection					x
Research Data Questionnaire				x	
Medical history		x		x	
Contacting GP/healthcare team				x	
Accessing Medical Records				x	

6.2 Recruitment

The recruitment phase will commence as soon as all necessary approvals have been received. Potential participants will be identified and/or contacted through the approaches described below.

6.2.1 Participant identification

i. **Via the direct healthcare team:**
IgAN patients with and without recent loin pain would be identified by the patients' direct healthcare team. These patients would be contacted by their healthcare team to give the study leaflet, containing a link/QR code to an invitation to contact (IoC) form.

ii. **Via social media:**
The study leaflet would be advertised in Leicester IgA Nephropathy patient groups on social media platforms, wherein interested participants would find a link/QR code to the IoC form.

iii. **Via distribution of the study leaflet at UHL:**
The study leaflet would be distributed at UHL, whereby interested participants would find a link/QR code to the IoC form.

The IoC form would contain a brief questionnaire to ask for contact details (title, name, e-mail, postal address, telephone number). This data would only be saved and shared with the research team once they click submit. The form would also contain the screening questionnaire on the next page if the patients wish to continue. If patients are automatically screened out on the screening questionnaire, all of their responses, including those on IoC, would automatically get discarded by JISC.

This form would be hosted by JISC Online Surveys.

6.2.2 Screening and eligibility assessment

The screening questionnaire will be accessed from the IoC form, and patients will be asked questions based on the inclusion/exclusion criteria detailed in Section 5.

6.2.3 Informed consent

PIS

Informed consent will be received from eligible participants after a discussion with a member of the Research team on the delegation log, before any research activities are conducted. The patients would be provided with the PIS virtually (via e-mail or post) before this discussion. The PIS would explain in lay language the study purpose & protocol, risks & benefits of participating, what taking part would entail, safety procedures to follow during visits, visit plan, and information about withdrawing from the study. Patients will be given as much time as needed to go through the PIS and talk to friends, family, and their healthcare team (at least 48 hours) before scheduling the informed consent discussion. The PIS would also include contact details for the research team, should they wish to clarify any doubts before the informed consent discussion.

Informed Consent Discussion –In Person

The informed consent discussion would involve a detailed explanation of the study, potential risks, and any preparations the patient would need to make before undergoing the MRI & sample collection. They would be clearly informed that they can withdraw from the study at any time, with or without giving a reason, and it would not impact their routine care. They would also be informed that the samples and data collected up to the point of withdrawal may be retained, but anonymity would be maintained in the publication of research data. Any questions that the patient may have regarding the study, taking part, visits, and withdrawing would be adequately answered. If any questions are beyond the scope of the present members of the research team, the member would reach out to the Chief Investigator and have these answered before obtaining written consent.

Informed Consent Discussion –Virtual

If the patient is unable to attend the informed consent discussion in person, a Microsoft Teams, Zoom, or phone call would be arranged. The process and information would flow just as mentioned above.

Written Informed Consent –In Person

Written informed consent will be obtained with the dated signature of the patient and the involved member of the research team. A copy of the consent form would be given to the patient, 1 x copy would be retained at the study site within the Investigator site file, 1 x copy to be filed in the medical records, and 1 x copy for sample transfer.

Written Informed Consent –Virtual (Online)

At the end of the discussion, the patient would be given a unique link to the e-consent form hosted on JISC surveys. The member of the research team involved would get the completed copy by email, which would then be authorised via email by them. Once this action is completed, the patient will receive the final copy of the signed and dated form in their email.

6.3 Randomisation

Not Applicable

6.3.1 Blinding and code breaking

Not Applicable

6.4 Study assessments

Information recorded on secured electronic forms (Invitation to contact form, screening questionnaire) -JISC Surveys

Contact Details

Screening Questions:

1. IgAN diagnosis, medications
2. Enrolment in other research studies

3. Other medical conditions, including other kidney diseases
4. Dialysis and kidney transplant information
5. Conditions/implants that may interfere with MRI participation
6. Loin Pain (nature of pain -intermittent/episodic or constant, and frequency)
7. Ability to differentiate between loin and musculoskeletal back pain

Information recorded on secured electronic forms (Research data questionnaire) -JISC Surveys

This questionnaire will be requested after informed consent is received.

Demographics:

1. Age range
2. Sex assigned at birth
3. Ethnicity
4. Height & Weight

Medical Details:

1. eGFR range, if known
2. Loin pain: pain description, location of pain, duration of pain, accompanying symptoms with pain)
3. Current medications

Medical Credentials:

1. NHS number
2. Full Name registered with GP
3. Home address registered with GP
4. Date of birth
5. GP details
6. Nephrologist details

In-Clinic Assessments

Study visits after informed consent is received:

1. Cohort B (IgAN patients with no history of loin pain) & Cohort A-Timepoint 2 (IgAN patients with no current episode of loin pain)
   Blood Pressure Reading:
   Blood pressure reading would be taken on-visit with locally sourced equipment. The measurement would be noted in the CRF.
   MRI (not part of routine care):
   Patients would be scheduled to come in based on patient, equipment, and personnel availability.

Patients would undergo a pre-defined MRI protocol that would look at kidney volume and morphology.
The patients would be given safety pointers in the PIS and would be briefed again at the visit.
Blood Collection (not part of routine care):
Patients would undergo venepuncture before or after the MRI (same visit) for laboratory analyses at UoL labs.
Urine Collection (not part of routine care):
Patients would donate urine before the MRI (same visit) for laboratory analyses at UoL labs.

2. Cohort A-Timepoint 1 (IgAN patients with a current episode of loin pain)
Patients will be asked to visit the hospital for the same assessments as described above, scheduled to occur within 72 hours of the onset of loin pain. To facilitate the timely scheduling of study visits, participants will be asked to notify the research team when they experience an episode of their usual loin pain.

If a participant contacts the research team reporting pain that is severe, atypical for them, or otherwise clinically concerning, the research team will not provide medical assessment or advice. Participants will be signposted to appropriate clinical services, including their GP, NHS 111 for urgent but non-life-threatening concerns, or 999 in the event of a medical emergency. Any study-related visits will be deferred until the participant has sought appropriate clinical assessment, where necessary.

In addition to the above assessments, at the visit, patients will be asked a few questions to assess pain. This will include questions about when the pain started, the current status of pain, pain intensity, nature of pain, location of pain, any painkillers taken, any accompanying symptoms, and whether they can differentiate this pain from back pain. The answers will be recorded on paper under the participant ID, with a copy included in the ISF, and a digital copy stored in a secure database. This will enable us to better interpret the results of MRI, urine and blood analyses.

MRI image analysis and reporting:
MRI images will be analysed by the research student, who will be adequately trained to do so. Any clinically significant incidental findings on the report would be forwarded to the patient's direct healthcare team.

6.4.1 Long-term follow-up assessments

Not applicable

6.5 Study intervention(s) and comparator(s)

6.5.1 Description of study intervention

Not Applicable

6.5.2 Description of comparator

Not Applicable

6.6 Expenses and benefits

Participants can claim travel expenses up to £15 to the hospital for study visits

6.7 Early discontinuation/withdrawal of participants

Each participant is legally allowed to withdraw from the study at any given time. They are not required to provide a reason for withdrawal, but if it is conveyed, the reason will be recorded.

The research team members on the delegation log can withdraw a participant from the study if:

1. They are not eligible, as discovered in the screening or at later stages
2. The consent is withdrawn
3. Loss of capacity to consent
4. Adverse event (related or unrelated to the study)

In the case of an adverse event, the study investigator would arrange optimal care and follow-ups until it has resolved.

The type of withdrawal and reason for withdrawal will be recorded in the CRF and on the subject enrolment log.

6.8 Definition of end of study

The end of the study will be marked by the completion of patient recruitment, MRI scans, sample collection, analytical laboratory techniques, and final data analysis.

7 Sample Handling

7.1 Arrangements for sample collection

Sample Types, Volume, and Containers

Whole blood (60 mL: 30 mL in an EDTA-coated tube, 30 mL in an uncoated tube) and Urine (up to 50 mL) will be collected from participants in sterile containers sourced locally by the site.

Sample Processing

Whole Blood: Whole blood would be processed into serum and plasma at the site (Glenfield Hospital), straight after collection. 30 mL of whole blood would be used to process plasma by centrifuging at 1500 x g for 10-15 minutes. The top layer of plasma would be transferred into another sterile tube and aliquoted into 1 mL matrix tubes for storage and eventual transportation to UoL labs in batches.

The remaining would be processed for serum by letting the whole blood clot for 30-60 minutes at room temperature and then centrifuging at 1500 x g for 10 minutes. The top layer of serum would be transferred into another sterile tube and aliquoted into 1 mL matrix tubes for storage and transportation to UoL labs in batches.

The processed and aliquoted serum and plasma tubes would be stored in a -80º freezer at Glenfield Hospital until enough samples are collected for transportation to the UoL labs on dry ice.

Urine: Urine will not be processed at the hospital site. It would be refrigerated at 4 °C until ready for transfer to the UoL labs on ice on the same day.

7.2 Arrangements for sample analysis

- The urine analyses (microscopy, mass spectrometry, and ELISA/Luminex assays) would happen at the UoL labs, Hodgkin building.
- Blood would be processed into serum and plasma, making it non-relevant material; however, urinary cells are part of the analysis, so unprocessed urine (relevant material) would be transferred to UoL.
- The study from patient recruitment to analysis will be based in the UK only. Patient samples would not be shared with any commercial/industry partners, and no transport outside of the UK will occur.
- Plasma and Serum would be immediately frozen at -80ºC in Glenfield Hospital and transferred to UoL in batches for lab experiments at a later date. Urine samples will be refrigerated at 4ºC in Glenfield Hospital. Urine samples would be transferred to UoL the same day, within 4 hours of collection. Microscopic analysis should happen within 12 hours for refrigerated urine, and the leftover will be spun, aliquoted, and frozen at -80ºC for lab experiments at a later date.
- Urine samples would be transported on ice, and aliquoted frozen plasma and serum on dry ice. The sponsor (UoL) will be responsible for transportation.
- Leftover samples will be stored for future ethically approved research, if consented. No animal research would be conducted using these samples.

7.3 Arrangements for sample storage

- Samples would be put in storage conditions (-80ºC for plasma/serum; 4ºC for urine) at the Glenfield Hospital as soon as possible (within 30 minutes) until they can be transferred to UoL (within 4 hours for urine).
- At UoL, plasma/serum and spun urine (non-relevant material) would be stored at -80ºC ± 10ºC for 10 years or as long as viable, whichever is shorter (throughout the study duration and for future research purposes).

7.4 Arrangements for sample destruction

Samples would be destroyed as per the guidelines set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act after 10 years or upon participant request, should they wish to withdraw consent.

8 Safety Reporting

The procedures with participants in this study involve non-invasive, non-contrast MRI scans, urine and blood collection, and questionnaires. Hence, no adverse events/reactions are expected, besides mild discomfort during venepuncture and the noise of MRI scanners.

8.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward and unintended medical occurrence (including an abnormal laboratory finding), symptom or disease in a participant, **whether or not it is considered related** to the study.
Adverse Reaction (AR)	Any untoward and unintended medical occurrence (including an abnormal laboratory finding), symptom or disease in a participant **which is considered related** to the study. The assessment of expectedness **must be** undertaken by a delegated medically qualified professional. Where an event could be considered possibly, probably or unlikely related to the study, for the avoidance of doubt, this should be considered related.
Serious Adverse Event (SAE)	Any untoward and unintended medical occurrence that meets the following serious criteria, **whether or not it is considered related** to the study: • results in death • is life-threatening^ • requires inpatient* hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity, or • is a congenital anomaly/birth defect • Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: ^The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	Any untoward and unintended medical occurrence that meets the above referenced serious criteria and, in the opinion of the delegated medically qualified professional, is believed to be **related (possibly, probably, unlikely)** to the study intervention.

Suspected Unexpected Serious Adverse Reaction (SUSAR)	Any untoward and unintended medical occurrence that meets the above referenced serious criteria and, in the opinion of the delegated medically qualified professional, is believed to be **related** to the study intervention. There are **no anticipated events** for this study; therefore, any events which are considered related will be considered unexpected.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

8.2 Expected Adverse Events/Reactions and Serious Adverse Events/Reactions

Expected events are medical occurrences which are known to occur based on the population/disease being studied. **Expected reactions** are medical occurrences which are known to occur as a result of the intervention being tested.

This study is observational in nature with no medical interventions involved. Therefore, we do not expect any occurrence of an adverse event/reaction due to the study

8.2.1 Expected Adverse Events/Reactions

Due to the nature of the study, we do not expect any adverse events. Adverse events/reactions that occur within 24 hours of the study visit and are deemed likely related to the study will be the only ones reported to the sponsor.

8.2.2 Expected Serious Adverse Events

Due to the nature of the study, we do not expect any adverse events. Adverse events/reactions that occur within 24 hours of the study visit and are deemed likely related to the study will be the only ones reported to the sponsor.

8.3 Reporting procedures for All Adverse Events/Reactions

All non-serious Adverse Events/Adverse Reactions occurring from the time of start of study until 24 hours after any study visits observed by the investigator or reported by the participant, will be recorded.

The following information will be captured on the adverse event log;

- Description of the event
- Date of onset
- End date
- Severity*
- Assessment of relatedness to study (not related or related; possibly, probably unlikely)
- Action taken

Follow-up information will be provided as necessary.

The relationship of the event to the study will be assessed and signed off by a medically qualified individual listed on the Delegation of Authority and Signature Log.

Events will be followed up on until resolution or the event is considered stable.

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the participant's removal from the study (or the study intervention/procedures). A participant may also voluntarily withdraw from treatment/the study due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end-of-study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

*The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

Only SAEs that occur within 24 hours of the study visit and are deemed likely related to the study will be reported to the sponsor. All SAE information will be recorded on an SAE form and sent to the sponsor. Additional information (e.g., follow-ups or corrections) will be outlined on a new form and sent to the sponsor.

8.4 Reporting Procedures for Serious Adverse Events/Reactions (SAE/R)

All Serious Adverse Events and Reactions occurring from the time of start of study until 24 hours after a study visit will be reported to rgosponsor@le.ac.uk immediately and within 24 hours of becoming aware of the event.

The relationship of the event to the study will be assessed and signed off by a medically qualified individual listed on the Delegation of Authority and Signature Log.

Events will be followed up on until resolution or the event is considered stable.

The SAE/SAR will be reported using the appropriate forms and according to the Sponsor SOP for reporting serious adverse events (S-1009). Additional information will be provided if requested to the Sponsor and the main Research Ethics Committee (REC).

Copies of all documentation and correspondence relating to SAEs will be stored in the ISF as appropriate.

Any event considered **related and Unexpected** to the study procedures will be reported to the relevant Research Ethics Committee concerned. Fatal or life-threatening events must be reported within 7 days, all other events within 15 days.

The CI will inform all investigators concerned of relevant information about related but unanticipated events that could adversely affect the safety of participants.

8.5 Reporting Urgent Safety Measures

The Sponsor, the CI or the local PI at a research site will take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety. If any urgent safety measures are taken, the CI/Sponsor will be

notified immediately, and in any event, no later than 3 days from the date the measures are taken. Written notice must be provided to the Sponsor and the relevant REC of:

- the measures taken
- reason these measures were taken
- the circumstances giving rise to those measures
- plan for further actions

9 Statistics and Analysis

The statistical analysis of data would be performed on specialised software like R Studio and GraphPad PRISM.

Data will be tested for normal distribution using Q-Q plots, and parametric or non-parametric tests like T-tests, Mann-Whitney U test, Wilcoxon signed-rank tests, and linear/logistic regression would be used for statistical analyses.

9.1 Sample size calculation

Since this is an exploratory observational study, with no reliable prior research data on loin pain in IgA Nephropathy, it was not possible to estimate the effect sizes. Hence, the sample size of (20 per group) is based on feasibility (funding and time), availability of participants (relatively uncommon disease in the UK), and technical constraints (MRI availability and cost). We plan on recruiting 20 patients who experience intermittent loin pain and 20 patients who have no history of loin pain.

These calculations are based on recommended figures in published studies suggesting the statistically ideal sample sizes for pilot studies. (22, 23) The sample size was also decided on by looking at that of similar studies with a renal MRI component. It was noticed that MRI studies for feasibility and reproducibility generally tend to include a sample size in the range of 11-50 per group. (24-26)

We have based our sample size on the primary objective, i.e., performing renal MRI, as it is expected to be the limiting factor.

9.2 Planned recruitment rate

We expect to invite 2-3 eligible participants per week to visit UHL (Glenfield or Leicester General Hospital) for informed consent discussion and final recruitment. However, since we are also making arrangements for remote consent (over Microsoft Teams), the number of recruited participants per week may go up to 5.

We will only be recruiting at 2 UHL sites -Glenfield Hospital (primary for study visits) and Leicester General Hospital (primary for recruitment). Some patients may also be recruited through social media adverts.

9.3 Statistical analysis plan

9.3.1 Summary of baseline data and flow of patients

- List of baseline variables:
  - Age (categorical) – expressed in age ranges
  - Sex (categorical) – expressed as Male, Female, Other
  - Ethnicity (categorical) -expressed as White, East Asian, South Asian, Black, Mixed/Other

- BMI (continuous) – expressed in Exact Number
- eGFR (continuous) – expressed in ranges
- Other medical conditions (categorical) – Yes/No for Hypertension and Diabetes
- Blood Pressure (continuous) – expressed in exact number

- Continuous variables would be presented as Mean ± Standard Deviation if normally distributed, or Median (Interquartile range) if not
  Categorical variables would be presented as counts and percentages
- Baseline variables will be compared between the two cohorts (intermittent loin pain versus no history of loin pain) using statistical tests like T-tests or Mann-Whitney U test for continuous variables and Chi-square test or Fisher's exact test for categorical variables

9.3.2 Primary outcome analysis

- Primary outcome measures will include qualitative (presence of oedema) and quantitative MRI parameters (renal T1 and T2 relaxation times, total kidney volume).
- Continuous variables will be reported as mean ± Standard Deviation or median (interquartile range -IQR), depending on data normality.
- For within Cohort A analysis, paired T-tests will be used to analyse normally distributed variables and Wilcoxon signed-rank tests for non-parametric data. Analysis between Cohort A and B would be done using the unpaired T-test (normal data) or the Mann-Whitney U test (non-normal data). Data normality will be checked using Q-Q plots.
- False Discovery rate (FDR) correction would be used for analyses involving MRI metrics to handle multiple comparisons. If <5% of the data is missing, complete case analysis would be performed; otherwise, multiple imputation may be used. Values ≥3 SD from the group mean (if the data is normally distributed) or group median (if the data is non-normal) will be inspected as outliers and only excluded if a technical/manual error is reported.
- Predefined subgroup analyses will primarily include comparison between intermittent loin pain patients (Cohort A) during a current pain flare versus no current pain. We would also do a secondary subgroup analysis: comparing all measures between patients with 60<eGFR and 60>eGFR in both cohorts.

9.3.3 Secondary outcome analysis

- Secondary outcomes include proteomic/lipidomic profiles from urine (LC-MS/MS) with target validation and additional protein measurements with ELISA/Luminex on urine, serum, and plasma, and urine microscopy results. For mass spectrometry, measures will include effect estimates (e.g., log2 fold-change) with 95% confidence intervals. Urinalysis data will be summarised as:
  <u>Quantitative</u>
  RBC and WBC counts per high-power field [mean ± SD or median (IQR)]
  <u>Qualitative</u>
  Presence/absence of casts (RBC, WBC, granular)
- Paired comparisons (between different timepoints in Cohort A patients) will use linear or generalised linear models appropriate for continuous or

categorical data. Unpaired comparisons (between Cohorts) will use linear or logistic regression. Non-parametric methods will be used for non-normal data.

- Multiple comparisons, missing data, non-compliers, and spurious data will be handled the same as above.
- Predefined subgroup analyses would remain the same as above.

9.4 Subgroup analyses

Subgroup analyses will primarily include comparison between intermittent loin pain patients (Cohort A) during a current pain flare versus no current pain. We would also do a secondary subgroup analysis: comparing all measures (qualitative and quantitative) between patients with 60<eGFR and 60>eGFR in both cohorts.

9.5 Adjusted analysis

The sample size is not large enough for confounding to be meaningful.

9.6 Interim analysis and criteria for the premature termination of the study

Not applicable.

9.7 Participant population

Since this is an observational study, there is no randomisation. The participant population will include IgAN patients with intermittent loin pain and without any history of loin pain.

9.8 Procedure(s) to account for missing or spurious data

If <5% of the data is missing, complete case analysis would be performed; otherwise, multiple imputation may be used.

9.9 Other statistical considerations.

Not Applicable.

9.10 Economic evaluation

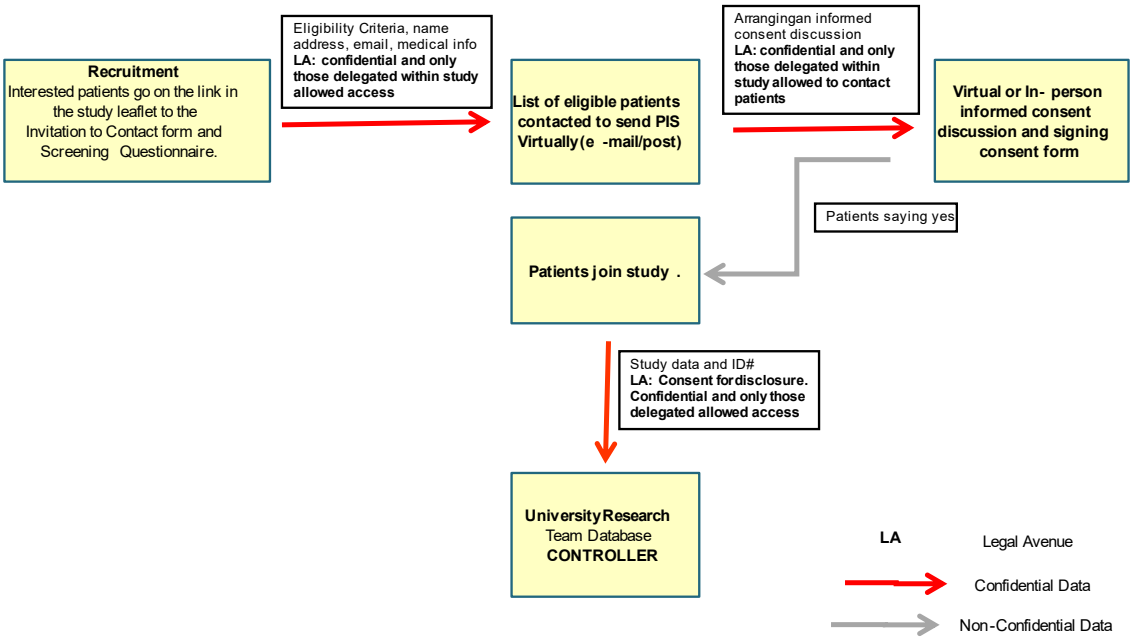
Not Applicable.

10 Data Management

Data Flow Diagram (Example)

Project Name: Mediators of Loin Pain in IgAN Date: 14/10/2025

Chief Investigator: Dr Haresh Selvaskandan IRAS ID: 364280



10.1 National data opt-out (this section is mandatory)

Not Applicable.

10.2 Source data

CRF data will be first recorded on the screening questionnaire, the research data questionnaire, and the pain assessment questionnaire. These include, but are not limited to, current medications and laboratory records.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g., there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

10.3 Data collection tools, handling and record keeping

Each participant will be assigned a unique identification number upon consent, and this will be added to all study documents/data collection tools in place of the participant's name.

The CRF and electronic database will refer to patients by participant ID. All documents will be stored securely and only accessible by study staff and authorised personnel. A copy of the completed participant informed consent form and participant

information sheet will be placed in the medical notes of all participants and in the Investigator Site File. All study visit summaries and AEs will be recorded in the hospital notes.

A contacts database (which contains participant contact details) will be held separately from the study database. Participants' contact details will be held securely in accordance with data protection regulations. This will be held in an access-controlled database at the University of Leicester. Contact details may be retained for up to 12 months after the study ends for participants who consent to receiving a copy of the research findings.

All data handling and record keeping will be kept in adherence to the University of Leicester and UHL policies. All study documentation containing identifiable patient data will be managed in accordance with ICH-GCP, the UK Policy for Health and Social Care Research and the Data Protection Act.

Study data will be stored on secure University of Leicester servers for 10 years after the study ends to verify results and for use in future ethically approved research studies, if consented.

10.4 Access to data

The Chief Investigator and relevant study staff will have access to the data collected as part of this research. Access to the study database will be restricted by role-based permission to authorised study personnel. All members will be suitably trained on the system before being granted access. Individual user accounts will be password-protected and will not be shared between members of the study team.

10.5 Archiving

Archiving of source data or the ISF for participating sites (Leicester General Hospital, Glenfield Hospital, and University of Leicester) will be arranged by the relevant participating site.

11 Quality Assurance Procedures

The study will be conducted in accordance with the current approved protocol, ICH GCP, the principles of the Declaration of Helsinki, relevant regulations and standard operating procedures (SOPs). The Principal Investigator (or their delegate) will be responsible for maintaining the Investigator Site File and ensuring it is kept 'inspection ready' at all times.

11.1 Monitoring, audit and inspection

The University of Leicester, as Sponsor, operates a risk-based monitoring programme to which this study will be subjected.

12 Protocol Compliance

12.1 Protocol deviations

A study-related deviation is a departure from the ethically approved study protocol or other study document or process (e.g., consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory

requirements. Planned deviations or waivers are not allowed; however, it is acknowledged that accidental protocol deviations may occur. Any deviations from the protocol will be documented in a protocol deviation form and filed in the Trial Master File/Investigator Site File as applicable.

If a protocol deviation occurs, then the CI (or delegate) will document this in accordance with the University's Standard Operational Procedure (SOP) Identifying and Reporting Deviations and Serious Breaches of GCP and/or the Protocol.

Deviations from the protocol which are found to frequently recur will be explored, and where necessary, an amendment to the protocol will be made.

12.2 Serious breaches

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor will be contacted within one working day. In collaboration with the CI, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

13 Ethical and Regulatory Considerations

13.1 Research ethics committee (REC) and regulatory review, approvals/permission/support, compliance and reports

Once the Sponsor Review process is complete, authorisation from the University of Leicester's Research Governance Office will be issued to book further regulatory review of the proposed research. The NHS Research Ethics Committee and the Health Research Authority will then review the proposal. Agreement in principle is subject to the research receiving all relevant regulatory permissions. Submission for regulatory approvals will occur via the Integrated Research Application System (IRAS). The Chief Investigator will ensure that all regulatory approvals, confirmation of capacity and capability from NHS sites and sponsor green light are in place before participants are approached.

For any required amendment(s) to the study, amendment will be submitted to the sponsor in the first instance for review and approval to submit the amendment for external regulatory approval. Amendments must be implemented following all required ethical, competent authority, site and Sponsor approvals and in line with Sponsor Standard Operating Procedures.

The Research Governance Office's Standard Operating Procedures will be followed for the duration of the study.

The Chief Investigator will notify the REC when the study has ended by completing the end of study notification form and will submit a final report of the results within one year after notifying the REC.

An Investigator Site File (per site) will be maintained for the duration of the study and will be stored for a minimum of 10 years after the study has ended. The only time this could be exceeded is if samples are being retained beyond the scope of the original study, i.e., there is consent for future research. In this circumstance, ICFs may be retained for as long as the samples are in existence, as we have a legal requirement to prove the samples were obtained with consent.

13.2 Peer review

The research has been reviewed by the academic supervisors.

13.3 Patient and public involvement

Prior to this study, our lab conducted a nation-wide survey for another project to understand the impact of loin pain in IgAN patients. We have used this as relevant existing PPI evidence. (3, 27)

Who was involved?	There was no exclusion based on location, but the PPI material was advertised on a Facebook group affiliated with Kidney Research UK and an IgAN patients' group based in Leicester. Hence, most of the data came from UK-based patients. 35 people responded to the survey, of which 29 were IgAN patients, 1 was not an IgAN patient, and the remaining 5 did not provide information on disease status.
How and when have they been involved?	We advertised a study design leaflet and a survey link on social media. The survey was hosted on JISC after the study protocol was finalised. The questions on this survey aimed to get patient and public opinion on the study purpose, importance, study description clarity, proposed procedures concerning patients, and overall suggestions/concerns.
How has the input of the people you involved made the study ethically acceptable?	Our survey retrieved the following results: 1. 100% of the respondents said that the purpose of the study makes sense to them. 2. 100% of the respondents thought that the research was important. 3. 86% of the people said that the explanation of loin pain was clear to them. 4. 94% of the respondents said that the study description was clear to them. The remaining 2 left the following comments: "The word loin, I think kidney pain would be

	better", and "the extent of pain, and the duration of pain were not mentioned". 5. 91% of the respondents said they feel comfortable with MRI scans if they were participating in the study. The remaining 3 left the following comments: "Severe loin pain was one of my earliest symptoms and preceded bloody urine. I have gone on to develop a more complicated medical history (as yet undiagnosed), multiple allergies to food and chemicals being one symptom. By staying off certain foods, I have managed to avoid the flares that I frequently used to get and have managed to stay relatively stable. To trigger a flare I would have to start eating those foods again which would cause other health issues and I feel I am now too old and the distance too far for me to travel. I am, however, happy for you to access my health records if you feel this would be helpful", "rather not have any unnecessary tests", and "I get claustrophobia in the scanner.". 6. 97% of the respondents said that coming in clinic for a study visit within 72 hours of experiencing loin pain was reasonable. Remaining 3% expressed concerns with work commitment. 7. 91% of the respondents expressed no concerns with blood and urine collection. The remaining 3 people left the following comments: "not being able to get a blood test at short notice", "consideration of where blood is taken to prevent potential collapse of veins in the future.", and "distance of travelling". 8. 91% of the respondents said that they will consider taking part in this study. The remaining 3 respondents left the following comments: "Live in Cumbria so unable to travel if not at local hospital", "I think it may be too far for me and I don't experience loin pain (except possibly very mild pain a few times)", and "In US". 9. 94% of the respondents said that they are comfortable to travel to the hospital when in pain for an MRI scan and sample donation. 10. 100% of the respondents said that they were comfortable with the research team accessing their health records to retrieve latest kidney function lab test results.

11. 100% of the respondents were comfortable with the research team informing the GPs of their participation in the study.
12. The following additional comments were left, when asked if there were anything else the research team should consider:
    i. "I am on dialysis and still get this"
    ii. "Locations for participation"
    iii. "I only occasionally experience loin pain. My egfr is 19. I live in south wales"
    iv. "I do not suffer from loin pain so don't think I am useful to you on this study"
    v. "Is this a geographically based study around the Leicester area only or open to UK wide participants?"
    vi. "Sometimes the pain is a constant dull ache, which can be difficult to determine, it is rarely more significant than that. Certainly never sharp or debilitating. I would also I correlate my hydration levels to the frequency of feeling any pain. Perhaps worth measuring hydration also."
    vii. "I think just defining loin pain clearly. I have a few times experienced very mild ache/discomfort in the kidney area of my back a few times but not to the point of being im pain. Is this loin pain?"
    viii. "Loin pain may be present even if kidney function is not lower than 50"
    ix. "All the nephrologists I have seen at UCH Plymouth (Derriford) have told me that IgAN does not cause pain and that any discomfort must be muscoskeletal in origin. With this in mind it would be helpful if the research team could facilitate patients with IgAN being able to request information to be sent to their local nephrology team or perhaps even offer some CPD for colleagues that have patients with IgAN."
    x. "I have crescentic IgA but am transplant ed not sure if that matters but I still have loin pain"
    xi. "Would kidney transplant recipients be allowed to be involved? I was

transplanted 18 months ago and still experience loin pain but much less often now I have a healthy transplanted kidney."

xii. "My loin pain occurs every 3-6 months and is debilitating for around 3-4 days which should fit with your 72hrs requirement."

xiii. "The survey doesn't mention if non IgA patient can take part."

Based on these suggestions, the following changes have been considered:

1. On patient recruitment material (the study leaflet):
   i. Loin pain has been clearly defined.
   ii. Broad inclusion and exclusion criteria for the study are included.
2. The screening questionnaire is designed to exclude patients who:
   i. Are claustrophobic in the MRI scanner and uncomfortable with participating in MRIs.
   ii. Are kidney transplant recipients.
   iii. Are on dialysis.
   iv. Experience constant or infrequent (less than once in 6 months) loin pain.
3. Patients will primarily be recruited in-clinic at Leicester General Hospital to reduce travel burden for study visits. In addition, patient-facing material would clearly mention that the study is based at UHL, hence patients may decline if travel is inconvenient.
4. The consent forms include taking consent from participants if they wish to opt in to receive a summary of overall research findings. At discretion, consenting participants may choose to share these general findings with their nephrologists. No individual clinical interpretation or medical advice will be provided.

13.4 Assessment and management of risk

Since this is an observational study developed with the help of qualified academic supervisors, there are no adverse risks.

Potential Minor Risks:

- Errors in venepuncture may cause bruising or soreness, which subsides in a short period of time. To avoid this, venepuncture will only be carried out by trained professionals.
- Our MRI protocol does not involve administering contrast agents, and MRI is inherently devoid of ionising radiation. However, we expect that some patients may experience claustrophobia. We will confirm in the screening questionnaire if patients are comfortable with MRIs (if ever done before). Patients will also be informed in the PIS and the consent discussion about the MRI protocol.

13.5 Data protection and patient confidentiality

The Chief Investigator will be the data custodian.

All information collected in the study will be kept strictly confidential.

The Chief Investigator and research team staff will comply with the requirements of the Data Protection Act and General Data Protection Regulation (and other applicable regulations) with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Analysis of the data generated will be undertaken by the Chief Investigator (or delegate) on the University of Leicester premises.

Consent forms, enrolment logs and details of record linkage* (i.e., participant ID numbers/pseudonyms) will be kept for a minimum of 10 years after the study has ended as part of the research data so that, in the event of the data being challenged, this will allow for verification of the quality of the data. At the end of this period, approval from the Sponsor will be requested for the destruction of the data.

While participants are taking part in the study, their contact details will be available to the researchers so that they can contact the participant to arrange the details of their research involvement. These will be deleted once they have been used for their agreed-upon purpose. Where individuals have consented to receive a copy of the research findings, contact details will be retained until this time. Contact details will be stored securely and separately from participants' research data and clinical information.

The Investigator Site File (ISF) will be kept at the relevant UHL site and will be stored in a secure environment. Storage will adhere to each organisational policy on storage.

Long-term storage will comply with the University of Leicester archiving Standard Operating Procedure.

13.6 Access to the final trial dataset

The CI and their appointed deputies will have access to the analysed trial dataset following execution of the SAP and completion of the End of Trial Report.

14 Finance and Insurance

14.1 Funding

This project is funded by an existing charitable donation made to our lab.

14.2 Indemnity

Sponsorship and insurance for study design and management will be provided by the University of Leicester.

If a participant is harmed due to negligence and/or the conduct of the study, this will be covered by the local NHS Trust(s) indemnity arrangements for all participants in clinical studies. If a study participant wishes to make a complaint about any aspects of the way they have been treated or approached during the research project, the standard National Health Service complaint system will be available to them. Details of this are made available to participants in the PIS.

14.3 Contractual arrangements

1. MRI scans at Glenfield Hospital will be paid for by the research team.
2. Time, consumables, and processing of collected blood and urine samples by Glenfield or Leicester General Hospital will also be paid for by the research team.
3. Courier services may be needed for the transfer of samples from UHL sites to UoL.

15 Dissemination

15.1 Dissemination Policy

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge the funder.

15.2 Authorship eligibility guidelines and any intended use of professional writers

Authorship will be determined in accordance with the ICMJE guidelines, and other contributors will be acknowledged.

Research participants will have the opportunity to receive a summary of the study findings. If they wish to receive a copy, this will be indicated on their consent form.

16 References

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