University Hospitals of Derby and Burton
NHS Foundation Trust

A feasibility study exploring the impact of a low Advanced Glycation End-product (AGE) diet on skin autofluorescence (SAF) levels in kidney transplant recipients.	
SHORT TITLE/ ACRONYM Kidney Transplant Low-AGE Diet Study (Transplant LAD)	
Version and Date of Protocol:	Version 1.0 – 09.09.2021
Sponsor:	University Hospitals of Derby & Burton NHS Foundation Trust
Chief Investigator:	Catherine Johnson Consultant Nurse Royal Derby Hospital Uttoxeter Road, Derby DE22 3NE. Phone: 01332 789354 Email: Catherine.johnson16@nhs.net
Local Reference:	UHDB/2020/018
IRAS Number:	298681
ClinicalTrials.gov number:	NCT05104242
Funder(s):	British Renal Society c/o Executive Business Support Davidson Road, Lichfield, Staffordshire WS14 9DZ Kidney Care UK 3 The Windmills, St Marys Close, Turk Street, Alton GU34 1EF
This protocol has regard for the HRA guidance	

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust, regulatory authorities, and members of the Research Ethics Committee.

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, and other regulatory requirement.

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 investigation 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; and that any discrepancies from the study as planned in this protocol will be explained.

Protocol Version 1 - 09.09.2021 authorisation signatures:

Chief Investigator:

Signature: Date:

…….. ……/……/……

Name (please print):

……..

For and on behalf of the Study Sponsor (if required):

Signature: Date:

…….. ……/……/……

Name (please print):

……..

Position:

……..

KEY STUDY CONTACTS

Chief/Principal Investigator:	Catherine Johnson Consultant Nurse Royal Derby Hospital Uttoxeter Road, Derby DE22 3NE Phone: 01332 789354 Email: catherine.johnson16@nhs.net
Co-Investigator(s):	Professor Maarten Taal Professor of Medicine and Honorary Consultant Nephrologist Academic Unit for Translational Medical Sciences, School of Medicine, University of Nottingham, Royal Derby Hospital, Uttoxeter Rd, Derby, DE22 3NE Phone: 01332 224618 Email: m.taal@nottingham.ac.uk; maarten.taal1@nhs.net Dr Janson Leung Consultant Nephrologist Royal Derby Hospital, Uttoxeter Road, Derby DE22 3NE Phone: 01332 789344 Email: janson.leung@nhs.net Dr Daniela Viramontes Hörner Post-Doctoral Research Fellow Academic Unit for Translational Medical Sciences, School of Medicine, University of Nottingham, Royal Derby Hospital, Uttoxeter Rd, Derby, DE22 3NE Phone: 01332 788262 Email: mszdv@nottingham.ac.uk
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Clinical Trials Unit:	Derby Clinical Trials Support Unit Medical School, Office 5033, Royal Derby Hospital, Derby, DE22 3DT Email: uhdb.DerbyCTSU@nhs.net
Statistician:	Not required, all statistical analysis will be performed by the investigating team

STUDY SUMMARY

Study Title:	**A feasibility study exploring the impact of a low Advanced Glycation End-product (AGE) diet on skin autofluorescence (SAF) levels in kidney transplant recipients.**
Local Study Reference:	UHDB/2020/018
Study Design:	This is a feasibility study consisting of 2 components: 1. A randomised controlled trial (RCT) to investigate the impact of a low AGE diet on SAF levels in kidney transplant recipients. 2. A nested qualitative interview study to assess the facilitators and barriers to adherence.
Study Participants:	Kidney transplant recipients who receive their transplant follow-up care at the Royal Derby Hospital
Planner Number of Sites:	Single site: The Royal Derby Hospital
Planned Sample Size:	**RCT** 40 kidney transplant recipients. Participants will be randomized in an unrestricted 1:1 ratio in random varying block sizes using a computer-generated random number into two groups: a) standard diet (control group) or b) low-AGE diet (intervention group). **Nested Qualitative Study** A sample of (n=15) participants will be purposefully selected; n=10 from the intervention group and n=5 from the control group.
Treatment Duration:	6 months
Follow-Up Duration:	No follow-up
Planned Start Date:	1st October 2021
Planned Recruitment End Date:	30th December 2021
Planned Study End Date:	30th December 2022
Research Question/ Aims:	Does a low-AGE diet reduce SAF levels and improve cardiovascular health in kidney transplant recipients? Specifically, this study will address: • Whether it is possible to conduct an RCT of the dietary intervention compared to a standard diet for kidney transplant recipients. • Determine whether the intervention is acceptable and participant views and experiences of the intervention.

FUNDING AND SUPPORT IN KIND

Funder(s)	Financial and Non-Financial Support Given
British Renal Society c/o Executive Business Support Davidson Road, Lichfield, Staffordshire WS14 9DZ	Joint BRS/KCUK grant Total Funding = £18,787
Kidney Care UK 3 The Windmills, St Marys Close, Turk Street, Alton GU34 1EF	Joint BRS/KCUK grant Total Funding = £18,787

ROLES & RESPONSIBILITIES

Sponsor

The Sponsor, University Hospitals of Derby & Burton NHS Foundation Trust, take on overall responsibility for appropriate arrangements being in place to set up, run and report the research project. A Division of Responsibilities between the Sponsor and the Chief Investigator (CI) will outline the delegation of certain responsibilities from the Sponsor to the CI.

Funder

The study is funded by a joint research grant from the British Renal Society and Kidney Care UK

Study Management Committees

Trial Management Group

The trial management group members are Catherine Johnson Chief Investigator, Dr Daniela Viramontes Hörner, Dr Janson Leung and Professor Maarten Taal. The group will meet monthly to oversee the day-to-day management of the trial, including all aspects of the conduct of the trial. Any problems with study conduct and participating centres will be raised and addressed during TMG meetings.

Protocol Contributors

A number of protocol contributors have been involved in the development of this protocol, these include Catherine Johnson the Chief Investigator, Co-investigators Dr Daniela Viramontes Hörner Post-Doctoral Research Fellow, Professor Maarten Taal and Dr Janson Leung and the Trial manager Rachelle Sherman.

Protocol contributors are responsible for inputting into the design of the study, ensuring that it is designed transparently and efficiently.

Contents

LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the study. Add or delete as appropriate to your study. Maintain alphabetical order for ease of reference.

AE	Adverse Event
AGE	Advanced glycation end-products
aPWV	Aortic Pulse Wave Velocity
BMI	Body mass index
CI	Chief Investigator
CKD	Chronic kidney disease
CRF	Case Report Form
ESKD	End-stage kidney disease
GCP	Good Clinical Practice
hsCRP	High-sensitive C reactive protein
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials
NHS	National Health Service
PI	Principal Investigator
PIS	Participant Information Sheet
RCT	Randomised Control Trial
REC	Research Ethics Committee
R&D	Research & Development
SAE	Serious Adverse Event
SAF	Skin autofluorescence
SGA	Subjective Global Assessment
SOP	Standard Operating Procedure
TMG	Trial Management Group
UHDB	University Hospitals of Derby and Burton NHS Foundation Trust

PROJECT GANTT CHART

Task name	2021				2022			
	Qtr 1	Qtr 2	Qtr 3	Qtr 4	Qtr 1	Qtr 2	Qtr 3	Qtr 4
Finalise study protocol								
Prepare study documentation								
Complete ethics application								
Await REC/HRA and R&D approvals								
Eligibility assessment/screening								
Recruitment								
Data collection/Study procedures and assessments								
Qualitative study interviews								
Data collation, analyses and dissemination								
Trial Management Group meetings								
PPI meetings								

STUDY PROTOCOL

1. BACKGROUND

Kidney transplantation is the optimal treatment option for end-stage kidney disease (ESKD). 35,823 adult patients had a functioning kidney transplant for ESKD in the UK on 31/12/2017, which represented 55.2% of the renal replacement therapy population. Transplantation is not only beneficial for the individual but also represents value to the greater health economy. The first year of care after a kidney transplant costs around £17,000 and £5,000 for every subsequent year compared to the average yearly cost of dialysis of £26,835 (UK Renal Registry, 2019).

Cardiovascular disease is the leading cause of death in persons with chronic kidney disease (CKD) including post-transplant. Whilst quality of life and clinical outcomes have improved in recent years, the survival of persons on dialysis remains poorer than that of many cancers. When compared to healthy subjects of the same age, persons receiving haemodialysis have a fivefold shorter life expectancy (Ardhanari et al., 2014). Reduced following kidney transplantation, this cardiovascular risk remains high with the greatest excess morbidity and mortality seen amongst youngest individuals (Jardine et al., 2011)

Advanced glycation end-products (AGEs) are a group of compounds formed by the non-enzymatic glycation of proteins, lipids or nucleic acids which progressively disrupt protein structure ultimately affecting tissue structure and function (Mallipattu et al., 2012). AGE formation in the body is increased by exposure to high glucose levels (in diabetes) and by inflammation and oxidative stress. In addition, AGEs may accumulate from exogenous sources including food (especially when cooked at high temperatures by baking, grilling, frying or roasting) and tobacco smoke (Uribarri et al., 2010; Arsov et al., 2014). AGEs are also produced normally in the body and their accumulation is a recognised manifestation of the normal aging process. Importantly, accumulation of AGEs has been highlighted as a risk factor associated with increased risk of cardiovascular mortality and morbidity (Meerwaldt et al., 2005; Shardlow et al., 2020).

The measurement of skin autofluorescence (SAF) is a validated non-invasive way to assess tissue accumulation of AGEs. SAF levels are a strong predictor of cardiovascular events in CKD (Shardlow et al., 2020) and of death and graft loss in transplant recipients (Hartog et al., 2006). Crowley et al. (2013) reported significantly lower SAF levels in kidney transplant recipients compared to persons on dialysis; however, these remained elevated when compared to the general population. In a small number of patients with pre-transplant measurements, a reduction in SAF was observed at a mean of 16 months post-transplant. However, there is still a lack of evidence in this area.

Due to the adverse outcomes associated with higher levels of SAF, several options focused on reducing the accumulation of AGEs have been proposed. One of these promising interventions is the reduction of dietary AGE intake. It has been suggested that cooking techniques that avoid very high temperatures such as poaching, steaming, stewing and boiling can significantly reduce the AGE content of food when compared to frying, broiling, grilling and roasting (Uribarri et al., 2010). Several randomized controlled trials (RCT) conducted in healthy overweight and/or obese volunteers

(Harcourt et al., 2011; Mark et al., 2014; Macías-Cervantes et al., 2015), persons with diabetes and the metabolic syndrome (Vlassara et al., 2002; Cai et al., 2004; Vlassara et al., 2016), and in those with CKD (Peppa et al., 2004; Vlassara et al., 2009) and performing peritoneal dialysis (Yacoub et al., 2017) have reported that restriction of dietary AGE intake is associated with a reduction in circulating AGE levels, suggesting that a low AGE diet may also be associated with a decrease in SAF.

2. RATIONALE

A systematic review (Clarke et al., 2016) concluded there was evidence to suggest that dietary modification to reduce dietary AGE intake was promising as an intervention to reduce AGE accumulation, highlighting the potential benefits of a simple dietary intervention in the prevention and treatment of chronic conditions. However, they noted that most of the evidence regarding dietary modifications to reduce exogenous AGEs is of low quality highlighting the need for further studies, which was of interest as this simple intervention is unstudied in kidney transplant recipients.

3. OBJECTIVES AND OUTCOME MEASURES/ ENDPOINTS

3.1. Objectives

The aim of this study is to establish the feasibility of conducting a definitive RCT which will investigate whether a low AGE diet leads to reduced SAF levels and improves cardiovascular health in kidney transplant recipients.

This innovative proposal is designed to test the feasibility of answering the question:

Does a low AGE diet reduce SAF levels and improve cardiovascular health in kidney transplant recipients?

Specifically, this study will address:

- Whether it is possible to conduct an RCT of the dietary intervention compared to a standard diet for kidney transplant recipients.
- Whether the intervention is acceptable, and participant views and experiences of the intervention.

Specifically, this study will address the following:

- Eligibility, recruitment and dropout rates, with reasons for loss to follow-up.
- Proportion of eligible participants recruited.
- The suitability and sensitivity of outcome measures for use in a larger trial.
- The most appropriate primary outcome measure for use in a larger trial and completeness of data.
- Estimates of the effects of the intervention to inform a sample size calculation for a larger trial.
- The feasibility of health economic data collection and preliminary cost data collection and calculations.

- The feasibility of delivering the intervention to the population group.
- Fidelity and adherence with the intervention.
- Determine whether the intervention is acceptable and participant views and experiences of the intervention.

3.2. Outcome

Primary outcome: SAF values at 6 months.

Secondary outcomes:

- Participant adherence to dietary intervention (achieving dietary AGE intake <8000 kilounits [kU]/day).
- Slope of SAF values over 6 months.
- Change in SAF values at 6 months.
- Change in weight over 6 months.
- Change in aortic pulse wave velocity (aPWV).
- Change in high-sensitive C reactive protein (hsCRP).
- Change in quality of life.

4. STUDY DESIGN

This is a feasibility study consisting of 2 components:

1. An RCT to investigate the impact of a low AGE diet on SAF in kidney transplant recipients.
2. A nested qualitative interview study to assess the facilitators and barriers to adherence.

5. STUDY SETTING

This study will take place within an NHS Renal outpatient setting at University Hospitals of Derby and Burton NHS Foundation Trust (UHDB).

6. ELIGIBILITY CRITERIA

Potential participants will be kidney transplant recipients who receive their follow-up care with the Transplant team at UHDB**.**

6.1. Inclusion Criteria

- Adults (>18 years) with a functioning (not on dialysis) kidney transplant.
- More than 12 months post-transplant.
- Able and willing to give informed consent.
- SAF levels above the general population mean value for age (Appendix 1).

6.2. Exclusion Criteria

- Persons with dark skin colour (i.e. Fitzpatrick skin colour type 5-6).
- Persons with malnutrition (Subjective Global Assessment [SGA] score $\leq$5).
- Pregnancy or breast feeding or intending pregnancy.
- Active infection.
- Active rejection.
- Persons with learning difficulties.
- Prisoners.

7. STUDY PROCEDURES

7.1. Recruitment

7.1.1. Patient Identification

Identification and enrolment of participants from the existing kidney transplant recipient population at The Royal Derby Hospital will be undertaken by the Chief Investigator Catherine Johnson, a member of the transplant team.

Initial contact will be made during a routine follow-up appointment. The initial details of the study and Screening Participant Information Sheet (PIS) will be provided by the usual care team (which may include the researcher). Participants will then be given ample time during their appointment to ask questions and consider whether they wish to participate with screening. Having obtained consent to screen Chief Investigator Catherine Johnson, a member of the transplant team will measure a SAF level. SAF level results are obtained within 3-5 minutes.

Participants with a SAF that is above the general population mean for age will then be invited to participate in the study. The Participant Information Sheet will be provided for the participants to take home. Participants will then be given ample time to ask questions and consider whether they wish to participate before being re-contacted by the Chief Investigator. If they do wish to participate, a further visit scheduled on the same day as their next routine appointment will be arranged to obtain consent and undertake baseline assessments.

It will be explained to the potential participant that entry into the study is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time. In the event of their withdrawal, it will be explained that their data collected so far cannot be erased and will be used in the final analyses where appropriate.

The participant's general practitioner will not be informed about the study because there are no implications for other aspects of treatment.

Participants will not be paid to participate in the study. Travel expenses will be offered for any hospital visits in excess of usual care. The majority of study assessments will be timed to take place at the time of routine visits, treatment or assessment.

7.1.2. Screening

Patient details will be assessed against the inclusion and exclusion criteria. Only those who meet the inclusion criteria and without exclusion criteria will be invited to participate.

At the initial contact visit outlined above, Chief Investigator Catherine Johnson, a member of the transplant team, will seek consent to measure SAF levels (i.e. consent to screen). Only patients with an SAF value that is above the general population mean for age will be invited to participate.

7.2. Consent

Consenting of participants will be undertaken by the Chief Investigator Catherine Johnson, or an appropriately trained and delegated member of the research team.

The process for obtaining participant informed consent will be in accordance with the Research Ethics Committee (REC) guidance, Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The Investigator has training and experience in assessing participant capacity and gaining informed consent in the clinical context.

Detailed information will be provided on the study to ensure that participants understand the purpose and potential risks involved. All participants will provide written informed consent. The Informed Consent Form will be signed and dated by the participant before they enter the study. The Investigator will explain the details of the study and provide a PIS, ensuring that the participant has sufficient time to consider participating or not. The Investigator will answer any questions that the participant has concerning study participation.

The decision regarding participation in the study is entirely voluntary. The Investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care.

Informed consent will be obtained from each participant before they undergo any interventions related to the study. Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the study (including the collection of identifiable participant data). One copy of this will be kept by the participant, one will be kept by the Investigator, and a third will be retained in the participant's hospital records.

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent according to the REC approved protocol and applicable guidelines and regulations.

7.3. The Randomisation Scheme

Participants will be randomised in an unrestricted 1:1 ratio in random varying block sizes using a computer-generated random number into two groups: a) standard diet (control group) or b) low

AGE diet (intervention group). Advice regarding both diets will be provided by an experienced dietitian. Both groups will receive precise oral and written instructions on how to follow the diets. Dietary advice will be individualised to patients' food preferences.

Standard diet (control group)
The standard diet will include energy intake of 30-35 kcal/kg of ideal body weight (IBW)/day (Mlinsek, 2016) and protein intake of 0.75 g/kg of IBW/day for females and 0.84 g/kg of IBW/day for males (Nolte Fong and Moore, 2018).

Low AGE diet (intervention group)
The low AGE diet will be the same as the standard diet in terms of calories (i.e. 30-35 kcal/kg/day) and protein (0.75-0.84 g/kg/day). However, it will reduce the dietary AGE content by changing cooking methods in food preparation to avoid exposure to dry heat such as frying, broiling, grilling and roasting, and to favour cooking with lower temperatures and high-water content as in stewing, steaming, boiling and poaching. In addition, the low-AGE group will be instructed to choose foods with low content of AGEs based on a food choice list that will contain examples of foods commonly available in the UK to be chosen as "allowed," "moderate intake," or "occasional." The goal will be to reduce dietary AGE intake to less than 8000 kU/day.

Dietary advice will be provided in person by an investigator with training and previous experience as a dietitian. Adherence to diets will be evaluated by means of a 3-day food diary (2 weekdays and 1 weekend day) every month. Monthly forms and written instructions on how to complete the 3-day food diaries will be sent by post to the participants. We will ask participants to return the completed food diaries in a pre-paid envelope. If needed, supplementary relevant diet information will be obtained by telephone consultation once the food diaries have been recorded and returned to the research dietitian.

There will be a follow-up meeting or discussion by telephone with participants randomised to the intervention group after 2 weeks of starting the study in order to reinforce the adherence and understanding of the intervention.

7.3.1. Method of Implementing the Allocation Sequence

The system to be used to coordinate randomisation is www.sealed envelope.com

The Chief Investigator, Catherine Johnson and Dr Daniela Viramontes Hörner will be aware of allocation which will be documented in the CRF (paper).

There is no expectation that randomisation codes will need to be accessed out-of-hours or in an emergency.

7.4. Study Assessments

Once eligible participants have read the PIS and given their informed consent, relevant participant characteristics will be extracted either from electronic data captured in medical records and from a self-reported questionnaire at baseline and will include demographic characteristics, educational level, employment status, duration of renal replacement therapy, transplant type and vintage, number of rejection episodes, aetiology of CKD, medical history (e.g. history of cardiovascular disease, diabetes and hypertension), current co-morbidities, alcohol history, smoking status and current medication.

The accumulation of AGEs will be assessed by measuring SAF using a validated Autofluorescence Reader Standard Unit version 2.4.3 (AGE Reader, DiagnOptics, Groningen, The Netherlands) at baseline, 3 and 6 months, as described in more detail elsewhere (Shardlow et al., 2020). In brief, the AGE Reader directs an ultraviolet excitation light (intensity 300-420 nm) through an illumination window of approximately 1 cm^2 on a skin area (free of visible vessels, scars, tattoos or any other skin irregularities) of the volar surface of the forearm at approximately 10 cm below the elbow. The AGE Reader then measures the amount of emitted light that is reflected back from the skin (intensity 300-600 nm) using a spectrometer (AVS-USB2000, Avantes Inc., Eerbeek, The Netherlands) and a 200-µm glass fibre. SAF is calculated by dividing the average emitted light intensity in the range between 420-600 nm by the average excitation light intensity in the range between 300-420 nm and expressed as arbitrary units (AU). Three measurements will be obtained and the average of these will be used for analysis. Valid SAF readings cannot be obtained when the skin reflectivity is lower than 6% (Mulder et al., 2006); therefore, persons with dark skin colour (i.e. Fitzpatrick skin colour type V-VI), who have an ultraviolet reflectance of less than 6%, will be excluded from this study.

Routine blood/laboratory tests will be performed at baseline, 3 and 6 months and will include haemoglobin, white cell count, hsCRP, glucose, HbA1C, urea, creatinine, potassium, phosphate, calcium, sodium, albumin, total proteins, cholesterol, triglycerides, intact parathyroid hormone and immunosuppression levels.

Nutritional assessments will be performed at baseline and at 3 and 6 months of treatment and will include: 3-day food diary (2 weekdays and 1 weekend day) to assess energy, fat and protein intake; a validated food frequency questionnaire to evaluate dietary AGE intake (Luévano-Contreras et al., 2013); the 7-point scale SGA for the classification of the nutritional status (well-nourished [SGA scores 6-7] or malnourished [SGA scores 1-5]); handgrip strength and anthropometric measurements and indexes, including weight, height, body mass index (BMI), mid-arm circumference, triceps skinfold thickness and mid-arm muscle circumference.

Cardiovascular evaluation will be performed at baseline, 3 and 6 months of treatment and will include traditional cardiovascular risk factors such as blood pressure, HbA1c, BMI and cholesterol. In addition, aPWV (a measure of arterial stiffness) will be assessed using the validated Vicorder device (Skidmore Medical, Bristol, UK) which is a predictor of cardiovascular mortality and morbidity (Lioufas et al., 2019).

Health-related quality of life will be evaluated at baseline, 3 and 6 months of follow-up with the EQ-5D-5L questionnaire.

Nested Qualitative Study

A sample of (n=15) participants will be purposefully selected; n=10 from the intervention group and n=5 from the control group, ensuring as far as possible that the sample includes a diverse representation of the study population for age, gender and ethnicity.

Potential participants will be given or sent an invitation letter and PIS, have the study explained to them and consented separately.

Semi-structured interviews will take place on completion of the intervention period broadly considering the acceptability and tolerability of the intervention in addition to the study process. These interviews will be facilitated by a trained researcher who is not a part of the clinical team to encourage free expression by the individuals involved. The interview will take place at a time and location convenient to the participants and will take about 60 minutes.

Data will be collected via digital audio equipment and transcribed by a Trust vendor qualified transcription service. Analysis will follow the conventions of framework analysis as outlined by Gale et al., 2013. Framework analysis involves a seven-stage process of coding and organising qualitative data in order to provide a structured interpretation of the data, which is finally presented in themes. The stages are: 1. Transcription, 2. Familiarisation with data, 3. Coding, 4. Developing a working analytical framework, 5. Applying the analytical framework, 6. Charting the data into the framework matrix, 7. Interpreting the data. The initial coding and development of the analytical framework will be in order to consensually develop the framework.

7.5. Schedule of Assessments

Study Procedures/Assessments	Screening	Recruitment	Baseline	Months						Post-intervention
				1	2	3	4	5	6	
Eligibility assessment	x									
Study discussed and PIS given		x								
Informed consent		x								
Randomisation		x								
Participant characteristics			x							
Skin autofluorescence	x		x			x			x	
Routine blood tests			x			x			x	
3-day food diaries			x	x	x	x	x	x	x	
Dietary AGE food frequency questionnaire			x			x			x	
Subjective Global Assessment			x			x			x	
Handgrip strength			x			x			x	
Anthropometric measurements			x			x			x	
Cardiovascular evaluation			x			x			x	
Quality of life questionnaire (EQ-5D-5L)			x			x			x	
Treatment adherence				x	x	x	x	x	x	
Qualitative study interviews										x
Adverse event assessments				x	x	x	x	x	x	
Physician's Withdrawal Checklist				x	x	x	x	x	x	

7.6. Withdrawal Criteria

Participants will be withdrawn from the study if they withdraw their consent at any point or decline to comply with the dietetic intervention or develop malnutrition. Female participants will be withdrawn from the study if they become pregnant.

Participants may be withdrawn from the study either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and will be used in the final analysis.

If participants fail to attend for their study visits, a member of the research team will try to contact them by telephone within 24 hours of their appointment and by written correspondence within a week of the missed appointment. Multiple attempts at contact will be made by the research team over a period of a month before stating that a participant has been lost to follow-up.

Data that is collected prior to withdrawal will be kept and analysed as part of the data set. The date, time and reason for participant withdrawal will be documented on the case report form (CRF).

7.7. Storage and Analysis of Samples

Routine blood/laboratory tests will be analysed in a local NHS laboratory at the Royal Derby Hospital, which is serviced and managed according to national standards and governance frameworks. Following analysis, samples will be destroyed according to local practice and no samples will be kept for longer than required for the study.

7.8. End of Study

The end of study will be defined as when the final patient attends for their last assessment. The CI will notify the Sponsor and REC within 90 days of the end of study. The clinical study report will be written within 12 months of the end of study.

8. SAFETY REPORTING

8.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant, including occurrences which are not necessarily caused by or related to study procedures.
Related AE	An untoward and unintended response in a participant to a study procedure. This means that a causal relationship between the study procedure and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or 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.
Related SAE	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the study procedures.

Related & Unexpected SAE	A serious adverse event that: • is believed with reasonable probability to be due to one of the study procedures. • the nature and severity of which is not consistent with the information provided in the protocol i.e. it is not listed as an expected occurrence.

8.2. Operational Definitions for (S)AEs

As a low-risk intervention, there is no requirement for non-serious AEs to be recorded or reported. Any AEs that meet the definition of serious (SAE) as per Section 8.1 and are not listed below must be reported.

Exceptions to SAE reporting:

- *Rejection*
- *Infection*
- *Graft Failure*
- *New Onset Diabetes after Transplantation*

The following circumstances are usually not considered SAEs:

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- Treatment, which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition.
- Any admission to hospital or other institution for general care where there was no deterioration in condition.
- Treatment on an emergency, outpatient basis for an event **not** fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

In all cases AEs and/or laboratory abnormalities that are critical to the safety evaluation of the participant must be reported. Where certain AEs are not required to be reported to the Sponsor (e.g. expected SAEs for the disease or intervention), these should be listed in the protocol and still be recorded in the participant's medical records.

8.3. Recording and Reporting SAEs

All AEs and SAEs must be recorded from the time of written informed consent until after the last visit. All (S)AEs occurring during the duration of the study must be reported by the investigator within the CRF. The PI is responsible for checking for AEs when participants attend for treatment and follow-up. All related and unexpected SAEs must be recorded by the investigator using the 'non-CTIMP safety report to REC form' from the HRA website. The completed form should be submitted to the Sponsor and REC within 15 days of the CI becoming aware of the event. Safety information will be reviewed during trial management group meetings.

UHDB contact information:
Email: uhdb.randdsae@nhs.net

8.3.1. Assessment of AEs and SAEs

8.3.1.1 Severity

The investigator should determine the severity of the AE:

- Mild: no interference with daily activities.
- Moderate: moderate interference with daily activities.
- Severe: considerable interference with daily activities (e.g. inability to work).

NOTE: to avoid confusion or misunderstanding, the term "severe" is used to describe the intensity of the event, which may be of relatively minor medical significance, and is NOT the same as "serious" which is described in the safety definitions.

8.3.1.2 Causality

Clinical judgement should be used to determine the relationship between the study procedures and the occurrence of each AE:

- Not-related: There is no evidence of a causal relationship between the event and study procedures.
- Related: There is evidence of a causal relationship between the event and study procedures i.e. a relationship to the study procedures cannot be completely ruled out.

Assessment of causality must be made by a medically qualified doctor (usually the PI).

8.3.1.3 Expectedness

The assessment of expectedness is only required if the event is deemed to be related to study procedures.

- Expected: Event previously identified and described in the protocol.
- Unexpected: Event not previously described in the protocol.

The expectedness assessment is delegated to Catherine Johnson.

8.4. Pregnancy reporting

If a participant becomes pregnant or is suspected to be pregnant from the time of consent up to the final study visit, they will be withdrawn from the study. There is no follow-up reporting required.

8.5. Reporting Urgent Safety Measures

If any urgent safety measure is taken, the research team should inform the Sponsor with 24 hours using the Sponsors safety incident reporting form. The Sponsor will inform the REC and participating sites of the measures taken and the circumstances giving rise to those measures within 3 days on implementation of the urgent safety measure.

9. DATA HANDLING

9.1. Data Collection Tools and Source Document Identification

Data will be collected on a CRF (paper) and transcribed onto an electronic database. CRFs will be stored as part of the ISF, which will be kept in a secure location with restricted access.

9.2. Source Data

For the purposes of this study, source data shall be defined as medical records of the participant (electronic or paper), any self-reported questionnaires and in some instances, the CRF may serve as its own source data for information collected directly from the participant.

9.3. Data Handling and Record Keeping

A validated spreadsheet (the database) will be developed and used for the transcription of data from the CRF, as described in the applicable SOP of the Sponsor. Validation will ensure data is entered in the correct format at the point of transcription in an effort to reduce transcription errors. The database will be stored on an NHS computer on a drive that is regularly backed up to a centrally hosted server (in the UK). Access to the database will be password protected and limited only to the appropriate members of the research team.

All data collected on the CRF and subsequently on the database will be pseudonymised, containing no identifiable data and using only a unique study ID to identify the study participant.

9.4. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections.

9.5. Archiving

At the end of the study, following completion of the end of study report, UHDB will securely archive all centrally held study related documentation for a minimum of 5 years. At the end of the defined archive period, arrangements for confidential destruction will be made. It is the responsibility of the Investigator to ensure that data and all essential documents relating to the study are retained securely for a minimum of 5 years after the end of study, and in accordance with national legislation. UHDB will notify the Investigator when study documentation may be archived, and then destroyed.

All archived documents must continue to be available for inspection by appropriate authorities upon request.

10. STATISTICS AND DATA ANALYSIS

Statistical analysis will be undertaken by Dr Viramontes Hörner with support from Prof Taal and Dr Leung. Data management and statistical analyses will be performed using statistical software SPSS version 26.0.

To compare baseline versus final evaluations, Wilcoxon test or paired t-test will be used in the case of dimensional variables, and McNemar test in the case of categorical variables. Intergroup comparisons will be performed using Mann Whitney test or Student t test for continuous variables and χ^2 test or Fisher's exact test for categorical variables.

10.1. Sample Size Calculation

As this is a feasibility RCT, no formal sample size calculation is required; however, the aim will be to recruit 40 kidney transplant recipients to test the study procedures and the feasibility of delivering the intervention. Power calculation using ClinCalc indicates that, assuming an SAF value of 2.81 ± 0.64 AU in the control group (Crowley et al., 2013), having a sample size of 18 in each group would give 80% power (α=0.05) to detect a difference in SAF of 0.6 AU between the groups at 6 months. The proposed recruitment would achieve this and allow for 10% drop-out.

10.2. Planned Recruitment Rate

This is a single centre pilot study aiming to recruit 40 adult (>18 years) kidney transplant recipients. This centre's kidney transplant recipient population numbers more than 300. With around 50 kidney transplant recipients attending for outpatient follow-up weekly, it is expected that the recruitment duration will be minimal.

10.3. Statistical Analysis

10.3.1. Summary of Baseline Data and Flow of Patients

Descriptive statistics will be presented to summarize the distribution of baseline variables across each of the randomisation groups. The continuous baseline variables (e.g. SAF, age, height, weight and blood pressure) will be reported with means and standard deviations, if shown to be normally distributed, using a combined skewness and kurtosis test, otherwise will be reported with medians and Interquartile Ranges (IQR). The categorical variables (e.g. sex, ethnicity and employment status) will be reported with frequencies and percentages.

A Consolidated Standards of Reporting Trials (CONSORT) flow diagram will be produced, showing the frequency of patients/participants:

- Assessed for eligibility or found eligible,
- Excluded before randomisation (and the frequency of each reason for exclusion),
- Randomised,

- Allocated to each randomisation group,
- That received each allocated intervention,
- That did not receive each allocated intervention,
- Lost to follow-up (and the frequency of each reason for loss to follow-up) for each randomisation group,
- Analysed for each randomisation group,
- Not analysed (and the frequency of each reason for not being analysed) for each randomisation group.

10.3.2. Outcome Analysis

Summary measures of all baseline variables will be calculated and reported. Primary and secondary outcomes will be compared between the two groups (Low AGE Diet vs. Standard Diet) at 6 months using a t-test if data are normally distributed or a Mann Whitney U test if not. Analysis will be by intention to treat.

10.4. Subgroup Analyses

Due to the limited number of participants, we will conduct only a single subgroup analysis by evaluating the results in participants with and without diabetes. Since diabetes is relatively common in kidney transplant recipients and may be a dominant factor affecting SAF in these people, it would be important to investigate whether a low AGE diet is effective in people with diabetes.

10.5. Adjusted analyses

As this is a feasibility study, we do not plan to conduct adjusted analyses.

10.6. Interim Analysis and Criteria for the Premature Termination of the Study

As this is a feasibility study with minimal risk of harm, we do not plan to conduct an interim analysis.

The Sponsor may suspend or prematurely terminate either the entire study, or the study at an individual site, for significant reasons that must be documented (e.g. an unacceptable risk to participants or serious repeated deviations from the protocol/regulations). If this occurs, the Sponsor shall justify its decision in writing and will promptly inform any relevant parties (i.e. participants, investigators, participating sites, REC, regulatory bodies).

10.7. Analysis Groups

The two groups for analysis will be the Low AGE diet and Standard diet groups. Analyses will be by intention to treat and will include all participants who were randomised and received at least one session of dietary counselling regarding their diet (all-treated population).

10.8. Procedure(s) to Account for Missing or Spurious Data

Missing data will be omitted from the analyses. The group sizes are too small to consider multiple imputations.

11. MONITORING, AUDIT & INSPECTION

The Investigator(s) must ensure that source documents and other documentation for this study are made available to study monitors, the REC or regulatory authority inspectors. Authorised representatives of the Sponsor may visit the participating sites to conduct audits/inspections.

Monitoring and source data verification will be conducted by the Sponsor according to their requirements, based on the risk assessment of the study. As a low-risk study, routine monitoring is not expected but may be conducted on an ad-hoc bases. The study may be audited by the Sponsor at any time, according to the Sponsor's audit programme.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1. Assessment and Management of Risk

The Sponsor has conducted the necessary risk assessment for this study and determined it as a low-risk study.

12.2. Peer review

This study has been peer reviewed as part of the British Renal Society and Kidney Care UK Research Grant application process.

12.3. Public and Patient Involvement

The Centre for Kidney Research and Innovation (CKRI) at UHDB NHS Foundation Trust has an established patient focus group that meets regularly to discuss all research projects and activities. This proposal was discussed at that meeting; the group felt that this was an interesting and important area to study; many gave their own anecdotes of their own and fellow patients experience of heart problems causing ill health and death. In addition, this project has been discussed with the more than 20 kidney transplant patients who participated in my MSc; these are the patients who have pushed for continued research in this area as they recognise the potential benefits for themselves and their fellow kidney transplant recipients. The focus group has agreed to review and feedback on this project, in addition to reviewing the study documentation and dissemination of its findings.

A member of the CKRI focus group is an advocate of co-production with both clinical staff and patients having an equal voice working together to create something new that meets everyone's needs and improves the lives of those who are affected by kidney disease and believes that utilizing this approach for this project will maximize its impact. Mr H. is especially supportive of this project

as he believes this is a novel research area that has potentially wide-ranging benefits for people affected by kidney disease and both the transplant and renal communities.

Mr H. is an academic with experience of research design including both qualitative and quantitative methodology and skills in academic writing. He is also under the care of the renal team at UHDB and as such has a specific interest in this research design. Mr H. was involved in the development of this application and will provide ongoing support in:

- Writing the plain English summary.
- Reviewing the study documentation (e.g. the PIS) and study processes (e.g. Recruitment strategies).
- Reviewing the appropriateness of the outcome measures.
- Contribute to the development of the intervention.
- Contribute to the development of the semi-structured interview.
- Will be involved in the analysis of the qualitative interviews by acting as a third coder.
- Contribute to the dissemination of the study.
- Contribute to the development of the definitive study.

It is recognised that Mr H will need to be appropriately reimbursed for his commitment and costs have been calculated in line with the INVOLVE Guidance (www.invo.org.uk)

12.4. Research Ethics Committee (REC) & Regulatory Considerations

The study will be conducted in compliance with the approved protocol and the Declaration of Helsinki. The protocol and all related documentation (e.g. informed consent form, PIS, questionnaires) will be reviewed by a Research Ethics Committee (REC). The investigator will not begin any participant activities until approval from the HRA and REC has been obtained and documented. All documentation and correspondence must be retained in the trial master file/investigator site file. Substantial amendments that require HRA and REC (where applicable) review will not be implemented until the HRA and REC grants a favourable opinion (with the exception of those necessary to reduce immediate risk to participants).

It is the responsibility of the CI to ensure that an annual progress report (APR) is submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, annually until the study is declared ended. The CI is also responsible for notifying the REC of the end of study (see Section 6.9) within 90 days. Within one year of the end of study, the CI will submit a final report with the results, including any publications/abstracts to the REC.

Before any site can enrol a patient into the study, confirmation of capacity must be sought from the site's research and development (R&D) department. In addition, for any amendment that will potentially affect the site's permission, the research team must confirm with the site's R&D department that permission is on-going (Section 12.10).

12.5. Protocol Compliance

The investigator is responsible for ensuring that the study is conducted in accordance with the procedures described in this protocol. Prospective, planned deviations and/or waivers to the protocol are not acceptable. Accidental protocol deviations may happen and as such these must be reported according to the Sponsors SOP. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action, and could potentially be classified as a serious breach.

12.6. Notification of Serious Breaches to GCP and/or the Protocol

A "serious breach" is a departure from the protocol, Sponsor procedures (i.e. SOPs), or regulatory requirements which is likely to effect to a significant degree –

(a) The safety or physical or mental integrity of the subjects of the study; or
(b) The scientific value of the study.

If a serious breach is identified, the investigator should notify the Sponsor immediately (i.e. within 1 working day) using the 'Non-CTIMP Notification of a Serious Breach' form. The report will be reviewed by the Sponsor and CI, and where appropriate, the Sponsor will notify the REC within 7 calendar days of being made aware of the breach.

12.7. Data Protection and Patient Confidentiality

The study will be conducted in accordance with the Data Protection Act 2018. The investigator must ensure that participant's anonymity is maintained throughout the study and following completion of the study. Participants will be identified on all study specific documents (except for the informed consent form and enrolment log) only by the participants study specific identifier (and initials if deemed necessary). This identifier will be recorded on documents, biological samples and the database. The Investigator Site File will hold an enrolment log detailing the study specific identifier alongside the names of all participants enrolled in the study.

All documents will be stored securely with access restricted to study staff and authorised personnel. Catherine Johnson will act as the custodian of the data generated in the study.

12.8. Financial and Other Competing Interests for the Chief Investigator, Principal Investigators at Each Site and Committee Members for the Overall Study Management

The CI, PI and all committee members have no conflicts of interest to declare.

12.9. Indemnity

As UHDB is acting as the research Sponsor for this study, NHS indemnity applies. NHS indemnity provides cover for legal liabilities where the NHS has a duty of care. Non-negligent harm is not covered by the NHS indemnity scheme. UHDB, therefore, cannot agree in advance to pay

compensation in these circumstances. In exceptional circumstances, an ex-gratia payment may be offered.

12.10. Amendments

Changes to the protocol will be documented in written protocol amendments. The Sponsor is responsible for deciding if an amendment should be deemed substantial or non-substantial. Substantial amendments will be submitted to the relevant regulatory bodies (i.e. REC, HRA) for review and approval. The amendments will only be implemented after approval and a favourable opinion has been obtained. Non-substantial amendments will be submitted to the HRA for their approval/ acknowledgment. Amendments will not be implemented until all relevant approvals are in place.

12.11. Access to Final Study Dataset

The Chief Investigator Catherine Johnson and Co – Investigators Professor Maarten Taal, Dr Janson Leung and Dr Daniela Viramontes Hörner will have access to the final dataset.

13. DISSEMINATION POLICY

13.1. Dissemination Policy

The aim of this dissemination plan is to ensure the impact of the new knowledge generated is maximized.

Findings will be disseminated in the following ways:

- Abstracts will be submitted to professional conferences including nationally at UK Kidney Week and The British Transplantation Society in addition to local meetings. Internationally at The American Society of Nephrology, The European Renal Association and The European Society for Organ Transplantation.
- We will work with our organisation's communication team to share the findings of this study across the organisation and more widely.
- We will utilise social media platforms to share our findings. We have an established Renal Team and CKRI twitter account accessed by both patients and staff to support this.
- Articles will be submitted to peer review journals.
- Via social media which I believe is an underutilized resource for engagement, recruitment and dissemination.
- The success of this work will also be used to promote the non-medical clinical academic career organizationally, locally and nationally through the National Institute of Health Research 70 at 70 network which the CI is a member of.

In addition, the findings of this study will be specifically shared with patients:

- The findings of this study will be disseminated via patient groups nationally such as Kidney Care UK and locally through the Derby Kidney Patients Association and the CKRI PPI group, in addition to the annual renal showcase.

- We will work with our organisations communication team to share the findings of this study, specifically to patients linking it to our patient facing website.

If this feasibility study is successful, we will submit a grant application (Research for Patient Benefit) to fund a large randomized controlled trial.

13.2. Authorship Eligibility Guidelines and any Intended Use of Professional Writers

The Chief Investigator Catherine Johnson and Co – Investigators Professor Maarten Taal, Dr Janson Leung and Dr Daniela Viramontes Hörner will be granted authorship on the final study report.

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15. APPENDICES

15.1. Appendix 1 – Reference values of skin autofluorescence per age group.

Age group (years)	Skin autofluorescence value (mean ± SD)
10-19	1.11 ± 0.20
20-29	1.53 ± 0.30
30-39	1.73 ± 0.42
40-49	1.81 ± 0.36
50-59	2.09 ± 0.36
60-69	2.46 ± 0.57
70-80	2.73 ± 0.55
>80	2.71 ± 0.44

Adapted from: Koetsier M, Lutgers HL, de Jonge C et al. (2010) Reference values of skin autofluorescence. Diabetes Technol Ther 12, 399–403.

15.2. Appendix 2 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made