A randomised controlled trial assessing the effectiveness and cost effectiveness of thrice weekly, extended, in-centre nocturnal haemodialysis versus standard care using a mixed methods approach: NightLife

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Declaration of HRA protocol template use

This protocol has regard for the Health Research Authority (HRA) guidance and order of content, in line with Version 1.1 (March 2016) of the HRA Protocol Development Tool.

Confidentiality Statement

All information contained within this protocol is regarded as, and must be kept confidential. No part of it may be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust, regulatory authorities and members of the Research Ethics Committee, by any Receiving Party to any Third Party, at any time, or in any form without the express written permission from the Chief Investigator and/or Sponsor.

SIGNATURE PAGE

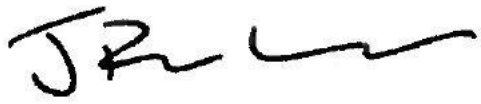
The undersigned confirms that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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.

Chief Investigator: Professor James Burton

Signature:



Date: 17/10/2023

Principal Investigator:

Print Name: _____

Signature: _____

Date: _____

Sponsor: University of Leicester

Print Name: Dr Cat Taylor

Signature:

Date:

KEY STUDY CONTACTS

Chief Investigator	Professor James Burton Professor of Renal Medicine Department of Cardiovascular Sciences College of Life Sciences Maurice Shock Building University of Leicester University Road Leicester LE1 7RH **Email:** jb343@leicester.ac.uk **Tel:** 0116 258 8043
Central Co-ordinating Centre	Leicester Clinical Trials Unit College of Life Sciences University of Leicester Maurice Shock Building University Road Leicester LE1 7RH **Email**: nightlife@leicester.ac.uk **Tel:** 0116 229 7243
Sponsor	University of Leicester Research Governance Office Leicester General Hospital Leicester LE5 4PW **Email**: rgosponsor@leicester.ac.uk **Tel**: +44(0)116 258 4099/258 4867
Funder	NIHR Health Technology Assessment (HTA) Programme Evaluations, Trials and Studies Coordinating Centre University of Southampton Enterprise Road Southampton SO16 7NS **Email:** netsmonitoring@nihr.ac.uk

PROTOCOL CONTRIBUTORS

Name	Position held	Role on study	Organisation
Professor James Burton	Professor of Renal Medicine	Lead applicant Chief Investigator	University of Leicester Department of Cardiovascular Sciences
Professor Laura Gray	Professor of Medical Statistics	Co-applicant Study design and statistics	University of Leicester Department of Health Sciences
Professor Gavin Murphy	Director	Co-applicant Trial governance	University of Leicester Leicester Clinical Trials Unit
Dr Helen Eborall	Lecturer in Critical Public Health	Co-applicant Qualitative research expertise	University of Edinburgh Usher Institute
Professor Patrick Mark	Professor of Nephrology	Co-applicant Clinical trials expertise	The University Court of the University of Glasgow Institute of Cardiovascular and Medical Sciences
Professor Nicola Cooper	Professor of Healthcare Evaluation Research	Co-applicant Health economic evaluation	University of Leicester Department of Health Sciences
Dr James Fotheringham	Honorary Lecturer	Co-applicant Health economic design and evaluation	University of Sheffield School of Health and Related Research
Professor Sandip Mitra	Honorary Professor	Co-applicant Dialysis expertise	University of Manchester Division of Cardiovascular Sciences
Madeleine Warren	Patient Advisor	Patient co-applicant	N/A
Dr Leila Rooshenas	Senior Lecturer in Qualitative Health Sciences	Co-applicant Oversight of QuinteT Recruitment Intervention	University of Bristol Population Health Sciences
Niamh Quann	Senior Trial Manager	Trial management	University of Leicester Leicester Clinical Trials Unit
Rachel Hobson	Head of Trial Management	Supporting role on grant application Oversight of trial management	University of Leicester Leicester Clinical Trials Unit
Dr Matthew GrahamBrown	NIHR Academic Clinical Lecturer Renal Medicine	Lead applicant and BHF CMR sub-study lead	University of Leicester Department of Cardiovascular Sciences
Dr Katherine Hull	NIHR Academic Clinical Fellow	Supporting role on BHF grant application Clinical Research Fellow	University of Leicester Department of Cardiovascular Sciences
Dr Victoria Cluley	Research Fellow	Qualitative researcher (workstream 2)	University of Leicester Department of Cardiovascular Sciences

Cassey Brookes	Principal Statistician	Statistical oversight	University of Leicester Leicester Clinical Trials Unit
Ghazala Waheed	Trial Statistician	Statistical analysis	University of Leicester Leicester Clinical Trials Unit

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ABBREVIATIONS

AE	Adverse Event
CDMS	Clinical data management system
CONSORT	Consolidated Standards of Reporting Trials
CRN	Clinical Research Network
DSMC	Data Safety Monitoring Committee
e-CRF	Electronic case report form
EQ-5D-5L	EuroQol EQ-5D-5L – Quality of Life questionnaire
ERA-EDTA	European Renal Association- European Dialysis and Transplant Association
ESA	Erythropoietin-Stimulating Agent
FPFV	First participant first visit
GDPR	General Data Protection Regulation
HD	Haemodialysis
HES	Hospital Episode Statistics
HRA	Health Research Authority
HTA	Health Technology Assessment
ICH-GCP	International Conference on Harmonisation Good Clinical Practice
INHD	In-centre nocturnal haemodialysis
ISD	Information Services Division
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number – clinical trial registry
KDQoL	Kidney Disease Quality of Life tool
LCTU	Leicester Clinical Trials Unit
LPLV	Last participant last visit
MedDRA	Medical Dictionary for Regulatory Activities
MCID	Minimal clinically important difference
NHS	National Health Service
NIHR	National Institute for Health and Care Research
ONS	Office of National Statistics
PPI	Patient and Public Involvement
PPIE	Patient Participation, Involvement and Experience
PSQI	Pittsburgh Sleep Quality Index
PTH	Parathyroid Hormone Test
QALY	Quality Adjusted Life Year
QoL	Quality of Life
QRI	QuinteT Recruitment Intervention
RCT	Randomised Controlled Trial
RDC	Remote data capture
REC	Research Ethics Committee
R&I	Research and Innovation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SIV	Site initiation visit
SONG-HD	Standardised Outcomes in Nephrology- Haemodialysis
SOP	Standard Operating Procedure
SRR	Scottish Renal Registry
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TTR	Time to Recovery
UKCRC	UK Clinical Research Collaboration
UKKW	UK Kidney Week
UKRR	UK Renal Registry
UoL	University of Leicester

KEY DEFINITIONS

- **Intervention arm:** Participants will receive 6-8 hours of in-centre haemodialysis delivered overnight, 3 times per week for 6-months. For the purposes of the protocol, this will be referred to as **nocturnal dialysis** throughout.

- **Standard care arm:** Participants will receive 3.5-5 hours of in-centre haemodialysis, 3 times per week during the day for 6-months. For the purposes of the protocol, this will be referred to as **daytime dialysis** throughout.

- **In-centre haemodialysis:** haemodialysis treatment in a hospital or dialysis clinic setting, where dialysis and needle insertion are generally provided by nursing or technical staff.

1. STUDY SUMMARY

Study Title	A randomised controlled trial assessing the effectiveness and cost effectiveness of thrice weekly, extended, in-centre nocturnal haemodialysis versus standard care using a mixed methods approach
Short Title	Does **NIGHT**-time dialysis improve quality of **LIFE**?
Study Acronym	NightLife
Study Design	Pragmatic, two-arm, multi-centre, randomised controlled trial with a health economic analysis. An internal pilot, an on-going process evaluation and a Quintet recruitment intervention are embedded in this study.
Randomised controlled trial (RCT) Eligibility	**Inclusion criteria** 1. Patients established on haemodialysis for >3 months (i.e. prevalent dialysis patients) 2. Age ≥ 18 years 3. Ability to give written informed consent 4. Ability to participate fully in the interventions and follow-up procedures **Exclusion criteria** **1.** Currently on in-centre nocturnal dialysis, or less than 3 months since stopping **2.** Less than 3 months since stopping extended daytime dialysis **3.** Patients for whom extended dialysis is clinically indicated (e.g. calciphylaxis, pregnancy) **4.** Scheduled for living donor kidney transplant **5.** Plan to change dialysis modality or centre in the next 6-months **6.** Life expectancy of <6-months **7.** Current participation in an interventional trial with conflicting therapies or primary outcomes
Randomisation	Participants will be allocated to an intervention group immediately after consent is taken using a randomisation process to either extended hours nocturnal dialysis or daytime haemodialysis (1.:1 ratio).
Recruitment sample size	216 participants (108 to the intervention arm and 108 to the control arm)
Study duration	60 months
Primary Outcome Measure	The primary outcome is the Kidney Disease Quality of Life (KDQoL) total score (calculated from the KDQoL-SF questionnaire) measured over 6-months.

Secondary Outcome Measures	1. Kidney Disease Quality of Life (KDQoL) total score (calculated from the KDQoL-SF questionnaire) measured at 1-, 3- and 6-months 2. Kidney Disease Quality of Life (KDQoL) domains (calculated from the KDQoL-SF questionnaire) measured over 6-months a) Physical component summary score (PCS) b) Mental component summary score (MCS) c) Kidney summary score (KSS) d) Kidney disease component summary score (KDCS) 3. Additional Patient Reported Outcomes measured at 1-, 3- and 6-months a) Health related QoL (EQ-5D-5L) b) Levels of fatigue (SONG Haemodialysis Fatigue measure) c) Sleep quality (Pittsburgh Sleep Quality Index) d) Time to recovery after dialysis e) Cognitive health (Montreal Cognitive Assessment) 4. Measures of safety a) Residual kidney function (urine collection and serum beta-2 microglobulin) b) Serious adverse events (SAEs) • SAEs in totality (rate/years) • Vascular access complications that lead to SAEs (rate/years) • Dialysis prescription changes that lead to SAEs (rate/years) c) Clinical outcomes (cardiovascular events, CVD death, mortality) (rate/years) 5. Measures of process a) Adherence to the intervention • Hours per session • Number of sessions missed • Number of sessions not meeting time criteria • Temporary change from treatment allocation b) Clinical results and dialysis parameters 6. Measures for cost-effectiveness analysis a) Resource use and expenditure questionnaire b) Cost per QALY gained

2. ROLE OF STUDY SPONSOR AND FUNDER

The study has been funded by a grant from the NIHR Health Technology Assessment (HTA) Programme (ref: NIHR127440). Additional support and resources for the study will be provided by the participating Trusts and their corresponding Clinical Research Networks (CRN). The funder will be responsible for funding the study but will not be part of the study conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

The Sponsor, the University of Leicester, will be responsible for all aspects of the study. The Sponsor will delegate duties to other parties, including Leicester Clinical Trials Unit (LCTU), this delegation will be formally documented. However, like the funder, the Sponsor will not be part of the study conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

3. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT GROUPS, OVERSIGHT COMMITTEES AND INDIVIDUALS

3.1 Trial Management Group (TMG)

The TMG will oversee the day-to-day running of the study and will meet according to the demands of the study, utilising conference calls for ease of attendance. There will be a central TMG based in Leicester to include the CI, Senior Trial Manager, Trial Manager, Trial Statistician, Research Administrator and co-applicants. In addition, according to the phases of the study, other collaborators with specific expertise will attend as appropriate. The TMGs will highlight any key day-to-day study issues and monitor progress of all research activity to ensure that project is being delivered to target. The TMG will provide input to the protocol and protocol amendment(s), recommend protocol amendments where applicable, ensure

the protocol is adhered to and take action as necessary to remedy any difficulties and consider and act on the recommendations of the Trial Steering Committee and Data Safety Monitoring Committee.

3.2 Trial Steering Committee (TSC)

An independent TSC* will be convened, with membership comprising of an Independent Chair, at least two Independent Members, two Lay Members, the Chief Investigator, LCTU Senior Trial Manager, Trial Manager and Trial Statistician. A Sponsor representative will also be invited to attend as a non-voting observer and provided with copies of meeting minutes. A TSC Charter will be put in place and 'Conflict of Interest' declarations obtained for all members and attendees. The TSC will be responsible for the scientific and ethical conduct of the study and will supervise progress of the study. The TSC members will be required to attend TSC meetings which will be held prior to the commencement of the study and annually or as required throughout the study.

3.3 Data Safety Monitoring Committee (DSMC)

An Independent DSMC* will be convened with its own Independent Chair, Independent Statistician and one other Independent Clinician. The DSMC will meet to monitor safety and effectiveness data every 12months, reviewing accumulating serious adverse events by arm, outcome data and accrual rates. The initial DSMC meeting will be held no later than 12 months from study commencement and meetings will also be held as necessary should any urgent issues occur. The DSMC will make recommendations to the TSC as to the continuation, extension of recruitment or follow up of the study. The decisions of the DSMC will be based on a report prepared by the Trial Statistician, the contents of which will be agreed by the DMSC members in advance who will adhere to a study-specific Charter. The DSMC will be responsible for the interests of the participants and its main role will be to make recommendations to the TSC.

**For the TSC and DSMC, independence is defined by the NIHR as follows:*

- *Not part of the same institution as any of the applicants or members of the project team;*
- *Not part of the same institution that is acting as a recruitment or investigative centre; •*

Not related to any of the applicants or members of the project team; • For the Chair only- not an applicant on a rival proposal.

3.4 Patient and Public Involvement (PPI)

Patients and the public have been involved in the concept, scope and design of this study from the very outset, and will be actively involved during the duration of the study.

Through consultation with the Leicester Kidney PPI Group, which comprises around 80 kidney patients, relatives and carers, the area of in-centre nocturnal dialysis was highlighted as a particular topic for priority, both in terms of service development and research. As a result, further pilots were started in additional Units (Kettering, Northampton), additional funding was secured to gain feasibility data to inform a future randomised trial and, a specific haemodialysis PPI group was established to seek advice about the scope and design of future dialysis trials. This group have met a total of 4 times over the last 2years and have informed the concept, design (including outcomes) of this study. Their input was invaluable in deciding on the individually randomised design and the inclusion of a workstream designed to evaluate attitudes towards recruitment and equipoise. In addition, it was the PPI panel that suggested we go further with our health economic modelling, to investigate the impact of dialysis on patients' carers and wider family, which could have financial and "wellbeing" implications within the whole community.

Madeleine Warren is a co-applicant for this study and will act as a non-independent, non-voting lay representative/expert patient on the TSC. In addition to Warren, an independent expert patient will join the TSC. Together, as our study PPI team, they will help to review the data, and contribute to the reporting and dissemination of the results.

A study-specific Patient and Public Involvement and Experience (PPIE) panel will be established from dialysis units where in-centre nocturnal dialysis is, and is not, offered. The purpose will be to:

- Act as the main channel of communication with patients at their respective dialysis units
- Inform the focus of observational work and key factors to explore in interviews
- Highlight known and potential problems in the set-up and delivery of in-centre nocturnal dialysis and continue to develop existing starter packs to maximise success in participating units
- Establishment and retention of the PPIE panel will be regularly reviewed by the CI and process evaluation lead.

Members of the PPIE panel will be offered training through their local Research Design Service workshops and through the NIHR INVOLVE Learning and Development Programme. This will give them the skills and confidence to review study documentation, take an active role in the TSC and help to disseminate the results.

By embedding the PPIE panel in this study, we will ensure the aims and objectives of the study remain focused on issues that matter to patients and the public and ensure that the work is disseminated to the general population rather than just the research and clinical community.

4. FLOW DIAGRAMS

Figure 1: Study Design - pilot and main RCT

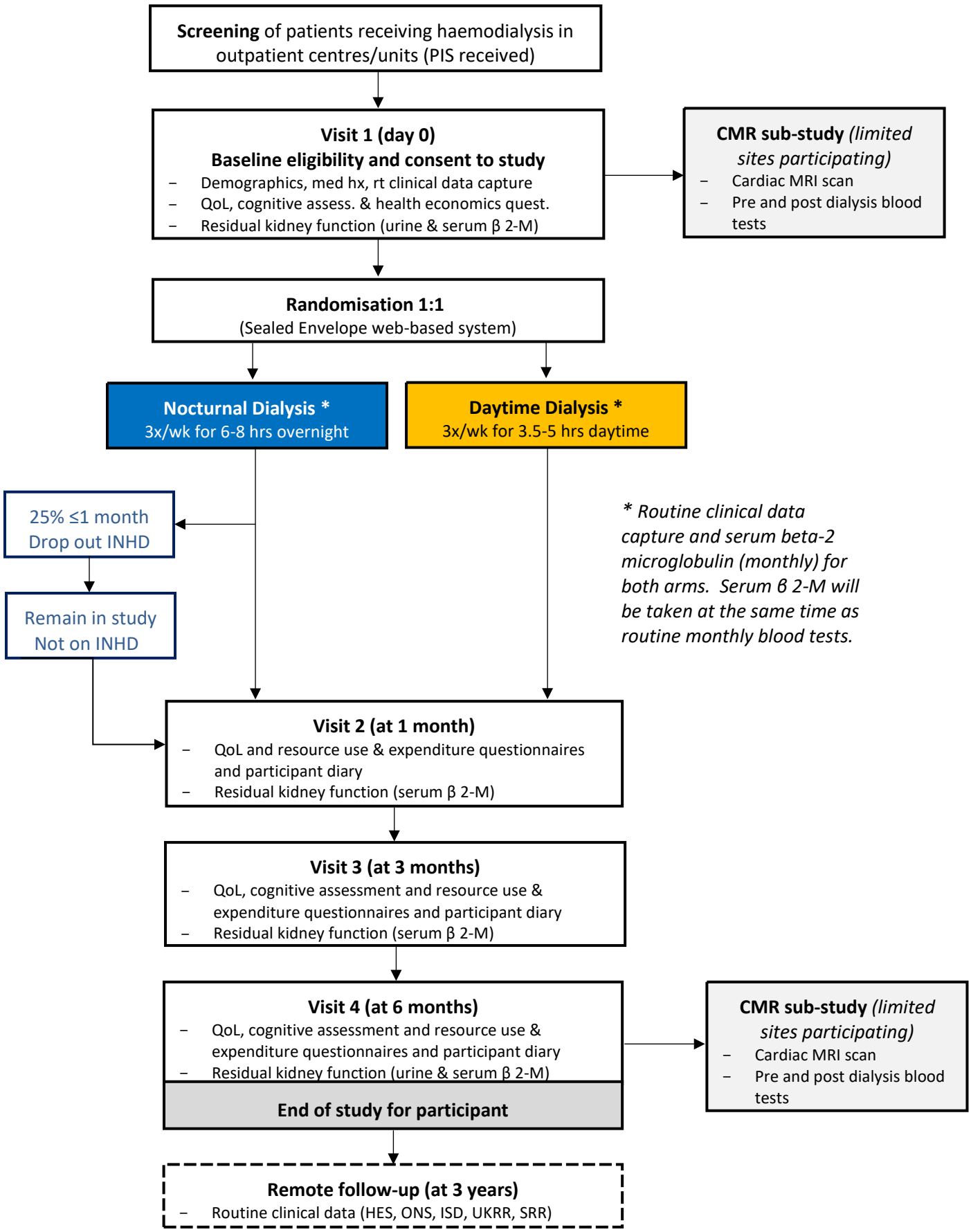
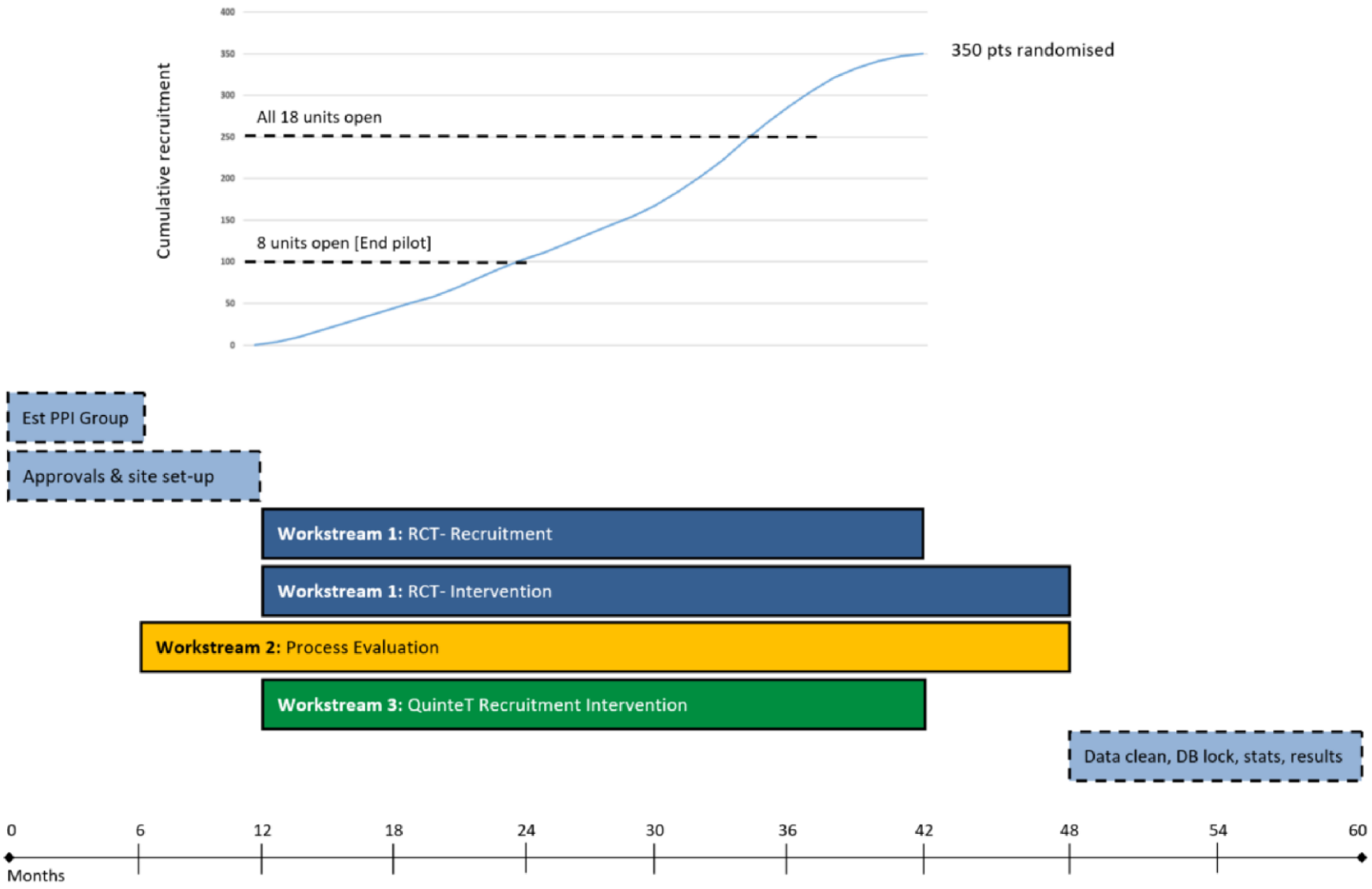


Figure 2: Workstream milestones flowchart



5. SCIENTIFIC ABSTRACT

Background: Haemodialysis (HD) can have extensive physiological, psychological and sociological impacts on patients. This is due not just to the physical side effects of HD but also the scheduling of treatment times, which results in patients 'losing' three days a week. Patient-reported quality of life is low, with many unable to continue paid employment. In-centre nocturnal HD offers patients the opportunity to dialyse overnight for longer while asleep. Despite growing evidence in support, it remains underutilised due to both equipoise in the renal community and uncertainty from commissioners about the cost benefit of implementation.

Aim: To measure the effect of a 6-month programme of extended hours, in-centre nocturnal haemodialysis (INHD) on quality of life.

Design: A pragmatic, two-arm, multi-centre, randomised controlled trial with a health economic analysis. An internal pilot, an on-going process evaluation (workstream 2) and a QuinteT Recruitment Intervention (workstream 3) are embedded in this study.

Randomisation: Participants will be allocated to an intervention group in the ratio 1:1. The randomisation algorithm with use minimisation to encourage balance between groups in terms of haemodialysis unit and age.

Target population: All prevalent adult patients receiving HD (or haemodiafiltration) in an out-patient hospital or satellite HD unit. Patients will be excluded if they: lack capacity to consent; have a life expectancy of less than, or are expecting a living kidney donor transplant within, 6 months; for whom allocation to standard hours care of 3.5-5 hours thrice weekly during the day would be clinically unacceptable.

Health technology assessed: Participants allocated to the intervention group will receive 6-8 hours of HD delivered overnight, three times per week for 6-months. Controls will receive daytime dialysis (3.5-5 hours three times per week during the day for 6-months). All other dialysis care will remain the same.

Objective: The overall aim of this study is to test the clinical and cost effectiveness of thrice weekly, extended hours nocturnal dialysis compared to standard dialysis care thrice weekly during the day.

Primary outcome measure: Patient reported quality of life over 6-months measured using the total score from the Kidney Disease Quality of Life tool (calculated from KDQoL-SF questionnaire).

Secondary outcome measures: Additional patient reported outcomes, safety and process measures, and measures of cost-effectiveness of the intervention.

Sample size: The study is powered to detect a standardised difference of 0.26 in the KDQoL between groups over 6-months adjusted for baseline. To achieve 90% power and a type I error rate of 5%, 216 participants are required, taking into account an overall attrition rate of 15%.

Analysis: The analysis will be by intention-to-treat. Point estimates and 95% confidence intervals from twosided tests will be calculated for all main outcome measures. A Statistical Analysis Plan will be drawn up prior to any analysis and reviewed by the Data Safety Monitoring Committee.

Timelines: Months 0-6: establish PPI group; Months 0-12: approvals and set-up; Months 12-24 internal pilot; Months 6-48: process evaluation, Months 12-42: QRI; Month 24: 8 units initiated; Month 38: all 18 units open; Months 48-60: data cleaning, database lock, statistical cleaning and dissemination of results.

6. LAY SUMMARY OF RESEARCH

Kidney dialysis is a lifesaving treatment for patients with kidney failure with around 24,000 patients receiving regular haemodialysis at a hospital or in a satellite clinic in the UK. Despite the benefits of receiving treatment, people with kidney failure who are on dialysis suffer from lots of intrusive symptoms

and ultimately their lives are shortened because of this devastating disease. Most patients have a set dialysis appointment time lasting for 4 hours, 3 times per week, with travel time in addition. This is mainly because it is convenient for the hospital and not the patient. Studies have shown that being treated with the dialysis machine for longer has benefits, but the hard fact is that medical teams struggle to schedule more flexible or extended dialysis schedules due to the volume of patients and finite numbers of machines and staff.

In-centre nocturnal haemodialysis offers patients something different; the opportunity to have their treatment overnight in a hospital or satellite dialysis clinic while they sleep. Studies suggest that people who have their dialysis overnight may live longer, feel better and may be able to live a life which is closer to normal. Because overnight dialysis (typically 6-8 hours) is a lengthier treatment, it rids the blood of more waste and excess water, acting more like a patient's normal kidneys which would be working 24/7. As it removes fluid more slowly, it also helps heart function. Importantly, it frees the person up during the day to socialise, work and care for others.

What we know about doing dialysis for longer isn't perfect though. People who choose to do more dialysis may feel better and live longer for other, completely unrelated reasons. The only way to know for sure is to compare longer treatment times overnight with the standard 4-hour daytime treatment in a well-designed clinical trial. Previous trials haven't always measured what matters to people with kidney failure which has made it difficult to assess the impact of a particular treatment on real lives. To make sure these mistakes are not repeated, the current study has been designed with the help of dialysis patients and medical teams from centres that are already offering overnight dialysis and also from those that don't.

This study asks the question whether six-months of overnight dialysis, performed three times a week in a hospital or satellite centre, improves the quality of life of patients with kidney failure, as compared to those who have shorter dialysis sessions during the day. People who are suitable and consent to take part (and who require dialysis for kidney failure) will be allocated at random to either nocturnal dialysis or daytime dialysis, which means their treatment will be determined by chance. This is done to create two groups of patients that are as similar as possible, allowing us to compare the two treatments fairly. Quality of life will be measured over the 6-months of treatment using questionnaires that have been specifically designed for kidney patients. We will also collect information on the extra costs of night-time dialysis, to see whether the new treatment is more cost-effective than conventional dialysis care, for the person and the health service. Finally, we will evaluate the experiences of patients who are enrolled in the study to identify barriers to how the treatment would become available across the NHS, if we were to find that it does benefit patients.

7. BACKGROUND AND RATIONALE

7.1 The impact on haemodialysis treatment on patients

Haemodialysis can have extensive physiological, psychological and sociological impacts on patients (1-3). This is due to the side effects of haemodialysis and also the scheduling of treatment times, which results in patients 'losing' three days a week. Unsurprisingly, patient-reported quality of life is low, with many patients unable to continue paid employment (4). Home haemodialysis, including dialysis overnight at home, is one way of offering flexibility for patients on regular dialysis but there are significant barriers for many patients (5). Alternatively, in-centre nocturnal dialysis involves patients dialysing for longer while asleep. There is, however, a need for further evidence to establish the effectiveness and cost-effectiveness of nocturnal extended dialysis compared with daytime dialysis (6).

7.2 Review of existing evidence

A recently published review of this topic by the Chief Investigator (6) which covers the existing evidence relevant to this study (and the knowledge gaps) in greater detail. This outlines the reason for equipoise within the renal community on the clinical utility of INHD and why it is only used in around 5% of dialysis facilities in the UK and worldwide.

The proposed research addresses the most important issues for HD patients. The SONG-HD initiative is a consensus exercise, endorsed by the international renal community, designed to highlight core outcomes for trials in HD (7). All of the top 10 core outcomes from this exercise; fatigue, dialysis adequacy, vascular access complications that lead to serious adverse events or hospital admission, cardiovascular disease and mortality, with patients rating dialysis free time, impact on family and ability to work (8) are evaluated in the current study.

As part of the ongoing evaluation of the nocturnal dialysis programme in Leicester, we have undertaken a number of quality improvement cycles to understand factors affecting the attrition rate of the in-centre nocturnal dialysis service in Leicestershire and to subsequently identify factors which may influence both the uptake and adherence (20). This led to the adoption of nocturnal dialysis 'starter packs' which will form part of the study intervention and the subsequent legacy by highlighting/confirming potential issues that implementation of in-centre nocturnal dialysis may cause and strategies with which to overcome them. This will aid recruitment and retention of patients and sites during the study and help to bridge the second translational gap of implementation into practice.

7.2.1 The effect of extended, nocturnal dialysis on quality of life

Observational data have shown that quality of life (QoL) outcomes are improved with nocturnal dialysis programmes, measured using a number of different instruments (9) but data from randomised controlled trials are less clear. The FHN Nocturnal Trial did not show a benefit in the co-primary outcome of death or QoL for patients undertaking NHHD (10). However, the sample size in that study was eventually reduced from 250 to 90 patients due to recruitment challenges, ultimately meaning that it was powered to detect much higher changes in QoL score which they did not achieve. The recently published ACTIVE Dialysis trial failed to show any improvements in QoL measured using the EQ-5D instrument in 200 patients randomised to either standard or extended dialysis (12 versus 24 hours per week) (11), these patients were predominantly dialysed during the day with only 10 participants in the extended group and 3 in the standard group dialysing overnight. The authors commented that the capacity of the EQ-5D to detect a meaningful improvement may have been limited.

We believe that these data highlight the need for the following:

- A randomised controlled trial to investigate the impact of in-centre nocturnal dialysis on quality of life
- The use of an alternative quality of life instrument that is more sensitive to the issues of patients with kidney disease which we address by using the Kidney Disease Quality of Life (KDQoL) score.

7.2.2 The effect of extended, nocturnal dialysis on clinical outcomes

The clinical benefits of nocturnal, extended hours dialysis have been explored in a number of large observational studies, with all studies suggesting similar, positive results (12-15) including improved fluid balance, cardiac stability and consequently, better blood pressure control. Conversely, there are also signals that extended hours dialysis may hasten decline in residual kidney function, a strong determinant of long-term survival (16), as well as reduce the lifespan of vascular access (23, 38).
This study addresses these by:

- Collecting data on the effects of in-centre nocturnal dialysis with mortality, cardiovascular events, and other clinical outcomes
- Evaluation of patients' residual kidney function due to the potential risk of declining kidney function with extended dialysis
- Assessing the effect of three-times a week extended dialysis on vascular access survival.

7.2.3 Cost effectiveness of in-centre nocturnal dialysis

No studies have formally assessed the cost-effectiveness of in-centre nocturnal dialysis programmes but concerns have been raised that in-centre nocturnal dialysis programmes may increase staffing costs due to increased dialysis times and anti-social hours supplements (17). However, there are potential societal economic benefits to in-centre nocturnal dialysis that may mitigate this e.g. reduced unemployment rates amongst incident dialysis patients (18). Indeed, a recent Cochrane review highlighted the provision of nocturnal dialysis therapies as a potential intervention to aid employment, not just for patients on dialysis, but also their carers (19).
These data highlight the paucity of information on the cost-effectiveness of in-centre nocturnal dialysis.
We will evaluate the cost-effectiveness by assessing the impact of the intervention on:

- staffing, consumables and other associated directly incurred overheads
- patient visits to healthcare professionals, hospital admissions including hospital length of stay, prescribed medication

We will also assess the impact of novel dialysis schedules on patients' and carers' ability to work.

7.3 Why is this research needed now?

This is an important, topical and timely research question for the NHS. The NHS Outcomes Framework for 2016/17 (21) outlines a number of priority areas for improvement in health outcomes which are directly relevant to this health question:

- Premature death in younger patients under 75 years of age;
- Enhancing quality of life for people with long term conditions by improving functional ability
- Reducing time spent in hospital and enhancing quality of life for patients and carers
- Ensuring that patients have a positive experience of care, especially in the out-patient setting, ensuring that provision of services is responsive to patients' needs.

This research question is vital to ensure that we offer to patients the broadest possible variety of options based on good evidence such that it improves outcomes whilst remaining cost-effective. Although there are a finite number of dialysis stations available within the NHS, good quality evidence will enable these to be utilised better.

The importance of research in this area is also reflected in the Kidney Research UK Strategy document prioritising improvements in quality of health / life and developing new approaches to address the burden of co-morbidity in patients with advanced renal disease (22). The most recent UK Renal Association HD guidelines acknowledge that although nocturnal schedules are not available in many centres, more patients should have access to longer duration dialysis (23). The European Best Practice Guidelines also advocate an increase in treatment time and/or frequency for certain patient groups (24) with the need for adequately powered trials which evaluate patient outcomes on more frequent HD modalities having been highlighted in recent reviews (25, 26).

8. STUDY DESIGN AND SETTING

This is a pragmatic, two-arm, multi-centre, randomised controlled trial with a health economic analysis. An internal pilot, an on-going process evaluation and QuinteT Recruitment Intervention are embedded in this study.

8.1 Aims and objectives

The overall aim of this study is to test the clinical and cost effectiveness of thrice weekly, extended hours nocturnal dialysis compared to standard dialysis care thrice weekly during the day. This will be achieved through the following objectives:

1. To determine the willingness and ability to recruit and randomise patients to thrice weekly, extended hours nocturnal dialysis during a 12-month internal pilot study
2. To measure the effect of extended hours in-centre nocturnal dialysis compared with daytime dialysis for patients with end-stage kidney disease on haemodialysis. This will be assessed using the Kidney Disease Quality of Life (KDQoL-36) questionnaire measured over 6 months
3. To measure the effect of extended hours in-centre nocturnal dialysis compared with daytime dialysis for patients with end-stage kidney disease on haemodialysis in terms of secondary outcome measures collected at 1-, 3- and 6-months post randomisation.
4. To assess feasibility and acceptability of in-centre nocturnal dialysis to patients and staff
5. To evaluate the cost-effectiveness of extended hours, in-centre nocturnal dialysis compared with daytime dialysis for patients with end-stage kidney disease within an NHS costing perspective
6. To understand and address issues that undermine RCT recruitment and informed consent during the QuinteT Recruitment Intervention

8.2 Study population

Adults with end-stage kidney disease who are receiving long-term (≥ 3 months) haemodialysis treatment in an outpatient facility will be invited to take part in this study. Patients will be recruited from 18 hospital and satellite haemodialysis centres and will include both NHS and commercial outpatient dialysis units; around 30% of out-patient dialysis care in the UK is delivered by commercial providers.

8.3 Outcome measures

8.3.1 Primary outcome measure

The primary outcome is the Kidney Disease Quality of Life (KDQoL) total score measured over 6-months. The KDQoL is a kidney disease specific measure of health-related quality of life across a number of domains. We have chosen this particular tool as it is the primary instrument used to assess quality of life in routine clinical practice globally, having been shown to have reliability and construct validity for the assessment of health-related quality of life among dialysis patients (27). The KDQoL is available in different formats; we are using the KDQoL-SF questionnaire. The KDQoL-SF questionnaire includes the generic Short Form-36 (SF-36) as its core with an additional 43 kidney-disease targeted items. The primary outcome (KDQoL total score) is calculated from a subset of data collected in the KDQoL-SF questionnaire.

The KDQoL incorporates four domains: physical component summary score (PCS), mental component summary score (MCS), kidney summary score (KSS) and the kidney disease component summary score (KDCS). The results for each of the dimensions are all generated from the data collected in the KDQoL-SF questionnaire. As well as being a sensitive measure of quality of life, each 1-point improvement in the PCS is associated with reductions in both the relative risk of death and hospitalisation by 2%. Similarly, a 1point improvement in MCS has been associated with a relative risk reduction for death of 2% and for hospitalisation by 1% (28). Given that there is an almost linear relationship between lower score and increased hospitalisation / mortality (29), a 5-point difference over 6-months in KDQoL physical score would associate with a 5-10% reduction, which we believe to be clinically significant. This 5-point

difference equates to a standardised difference of 0.26. All of these have been highlighted by SONG-HD as priority outcomes and we can therefore be confident that it measures what is most important to dialysis patients.

8.3.2 Secondary outcome measures

1. Kidney Disease Quality of Life (KDQoL) total score (calculated from the KDQoL-SF questionnaire) measured at 1-, 3- and 6-months
2. Kidney Disease Quality of Life (KDQoL) domains (calculated from the KDQoL-SF questionnaire) measured over 6-months
   a) Physical component summary score (PCS)
   b) Mental component summary score (MCS)
   c) Kidney summary score (KSS) - Average of symptoms, effects and burden domains
   d) Kidney disease component summary score (KDCS) – average of the 11 ESRD specific domains
3. Additional Patient Reported Outcomes measured at 1-, 3- and 6-months
   a) Health related QoL (EQ-5D-5L)
   b) Levels of fatigue (SONG Haemodialysis Fatigue measure)
   c) Sleep quality (Pittsburgh Sleep Quality Index)
   d) Time to recovery after dialysis
   e) Montreal Cognitive Assessment (MoCA, baseline, 3- and 6-months)
4. Measures of safety
   a) Residual kidney function (urine collection and serum beta-2 microglobulin)
   b) Serious adverse events (SAEs)
      - SAEs in totality (rate/years)
      - Vascular access complications that lead to SAEs (rate/years)
      - Dialysis prescription changes that lead to SAEs (rate/years)
   c) Clinical outcomes (cardiovascular events, CVD death, mortality) (rate/years)
5. Measures of process
   a) Adherence to the intervention
      - Hours per session
      - Number of sessions missed
      - Number of sessions not meeting time criteria
      - Temporary change from treatment allocation
   b) Clinical results and dialysis parameters
6. Measures for cost-effectiveness analysis
   a) Resource use and expenditure questionnaire
   b) Cost per QALY gained

EQ-5D-5L: this will be used to determine health state descriptions for the five components combined with preference-weighted health-related quality of life index scores (as approved by NICE) to generate Quality Adjusted Life Year (QALY) profiles for the cost-effectiveness analysis (30).

Other patient reported measures: not all outcomes that are important to dialysis patients are captured by the KDQoL and the EQ-5D-5L, the most important being fatigue (7). We will capture important aspect of fatigue in both groups in three ways:

- Asking patients a simple question on Time to Recovery (TTR) in minutes after dialysis is a simple measure of fatigue related to treatment that is reliable, valid and sensitive to change in daytime dialysis and nocturnal dialysis patients (34).
- The Pittsburgh Sleep Quality Index (PSQI) is a validated tool used to assess sleep quality in dialysis patients and has been used in this context to examine the association between sleep and lower health related quality of life scores (35).

The SONG-HD Fatigue Score – has been specifically developed to measure fatigue in dialysis patients (36). It consists of a visual analogue scale as well as three likert scale questions pertaining to tiredness, lack of energy and usual activities.

Cognitive assessment: the Montreal Cognitive Assessment (MoCA) is a validated tool for assessing cognitive health and can be used in individuals on maintenance haemodialysis (58). The MoCA will be used to objectively compare the impact on cognitive health for the standard care (daytime haemodialysis) and the intervention (nocturnal haemodialysis) arms. Each follow-up point will have a slightly different version of the MoCA (version 8.1 at baseline, 8.2 at 3-months and 8.3 at 6-months to avoid any learning-effect from influencing the results. All staff administering and scoring the MoCA will be required to undertake a mandatory online training and certification programme, to ensure the process is standardised and consistent amongst multiple raters.

Participants and research teams will have the option to complete the questionnaires (except the MoCA) over the telephone to assist with data collection and to enhance convenience for the participant. For example, for some, it may be preferable to minimise in-person data collection during a nocturnal dialysis shift to maximise the time available for the participant to rest.

Residual kidney function: extended dialysis may hasten decline in residual kidney function and impact on patient survival (37). We will record residual kidney function using urine collection with paired blood samples taken at the time of dialysis to give standard measures of urine volume, urea and creatinine clearance. Urine collection will be performed at baseline and 6-months only so as to minimise the impact and inconvenience to patients. In addition, a serum sample will be collected at the same time as routine monthly blood tests to measure beta-2 microglobulin, a validated surrogate for residual kidney function in haemodialysis patients (38, 39); thus enabling an accurate assessment with minimal inconvenience to patients.

Serious adverse events: in addition to standard serious adverse event reporting (see section 11 below), sites will record the number and type of serious adverse events (including mortality, cardiovascular events, hospitalisation and vascular access interventions). Hospital Episode Statistics (HES) and Office of National Statistics (ONS) databases (or equivalent, e.g. Information Services Division for Scottish sites) will be utilised for the 3-year follow-up data.

Measures of process: Adherence to the intervention (number of sessions attended and number of minutes), haemodynamics (ultrafiltration volume and pre-dialysis blood pressure), monthly blood results (dialysis efficiency [e.g. urea reduction ratio and Kt/V], haemoglobin [including ESA and iron prescription], ferritin, calcium/phosphate/PTH) will all be recorded from the same dialysis session as the collection of routine monthly bloods, using the e-CRF.

9. PARTICIPANT ELIGIBILITY CRITERIA

9.1 Inclusion criteria for RCT (workstream 1)

1. Patients established on haemodialysis for ≥ 3 months (i.e. prevalent dialysis patients)
2. Age ≥ 18 years
3. Ability to give written informed consent
4. Ability to participate fully in the interventions and follow-up procedures.

9.2 Exclusion criteria for RCT (workstream 1)

1. Currently on in-centre nocturnal dialysis, or less than 3 months since stopping
2. Less than 3 months since stopping extended daytime dialysis
3. Patients for whom extended dialysis is clinically indicated (e.g. calciphylaxis, pregnancy)
4. Scheduled for living donor kidney transplant
5. Plans to change dialysis modality or centre in the next 6-months
6. Life expectancy of <6-months
7. Current participation in an interventional trial with conflicting therapies or primary outcomes

These inclusion and exclusion criteria have been selected to be pragmatic and to therefore maximise external validity of the study. All adult patients who have been on dialysis for ≥3 months are eligible for inclusion; 3-months is the accepted cut-off after which it is unlikely new starters on dialysis will recover long-term kidney function. The exclusion criteria seek to address (and mitigate) three different potential sources of bias: those patients that are unlikely to complete the full 6-month intervention due to death or transplantation; patients who have a recognised clinical need for extended hours dialysis and may therefore not adhere to their allocated group (e.g. pregnancy, calciphylaxis) and; other factors outside daytime dialysis that may influence the primary outcome (e.g. participation in another interventional trial with QoL as a stated outcome measure or previous participation in a nocturnal dialysis programme).

9.3 Additional eligibility criteria for process evaluation (workstream 2)

9.3.1 Staff participant inclusion criteria

1. Clinical and non-clinical staff working at haemodialysis units participating in the Nightlife study
2. Age ≥ 18 years
3. Ability to give written informed consent
4. Ability and willingness to participate fully in the observations and interviews

9.3.2 Staff participant exclusion criteria

1. Age <18 years
2. Unable to give written informed consent
3. Unable or unwilling to participate in the observations and interviews

9.3.3 Relative/visitor participant inclusion criteria

1. Relatives or visitors accompanying patients (that fulfil RCT eligibility criteria) to haemodialysis sessions
2. Age ≥ 18 years
3. Ability to give written informed consent
4. Ability and willingness to participate fully in the observations and interviews

9.3.4 Relative/visitor participant exclusion criteria

1. Relatives or visitors accompanying patients that do not fulfil the RCT eligibility criteria 2. Age <18 years

3. Unable to give written informed consent
4. Unable or unwilling to participate in the observations and interviews

9.4 Additional eligibility criteria for QRI (workstream 3)

9.4.1 Staff participant inclusion criteria

1. Clinical and non-clinical staff working involved in overseeing or recruiting to the Nightlife study
2. Age ≥ 18 years
3. Ability to give informed consent

9.4.2 Staff participant exclusion criteria

1. Age <18 years
2. Unable to give informed consent

10. STUDY PROCEDURES

10.1 Participant identification and recruitment for pilot and main RCT (workstream 1)

A member of the clinical team will screen eligible patients in outpatient clinics of prevalent haemodialysis population (both NHS and commercial), satellite haemodialysis centres or dialysis units. A brief tri-fold information leaflet will be routinely distributed to patients at the same as their monthly blood reports, to make them aware of the study and that their dialysis unit is a participating site. Potential participants will be approached by a member of the clinical team (who by default, may also be a member of the research team) who will discuss and explain the study during the patient's routine outpatient dialysis visit.

Patients who express an interest in the study will be given a Participant Information Sheet (PIS) detailing the exact nature of the study, what it will involve for the participant and any risks involved with taking part. They will then be offered the opportunity to discuss the study in more detail with a member of the research team and ask questions, and allowed until their next dialysis clinic visit (typically between 36 and 48 hours) to decide whether to participate.

A screening log will be designed to identify trends and capture numbers of patients screened, eligible, approached, randomised, and numbers accepting their randomised allocation. These logs will be used as a tool in the QuinteT Recruitment Intervention to optimise recruitment. Patients will not be identifiable from the screening log.

The recruitment phase will commence once ethical favourable opinion, HRA approval, local Trust confirmation of capability and capacity and Sponsor 'green light' have been issued. It is anticipated that 216 participants will be recruited from 18 sites across the UK. The QRI (see section 11.7) will be integrated throughout the RCT recruitment period to optimise recruitment and informed consent, including issues relating to equipoise and patient/clinician treatment preferences.

10.2 Baseline assessment

Written informed consent will be taken by an appropriately qualified individual at sites, prior to undertaking the baseline assessments. Prior to randomisation, but after consent, participants will be asked to complete a number of questionnaires, detailed in Table 1. All participants will be asked for consent to access to their medical records and to link their research data to routine health data which will include: UKRR, HES, ONS and ISD data. Participants will consent to their identifiable data from participating sites being securely transferred to the Sponsor institution for subsequent linkage. Permission will also be sought to inform the participant's GP of their participation in the study.

Table 1: *Schedule of assessments*

	Screening	Baseline	1-month	2-months	3-months	4-months	5-months	6-months	3-years
Review eligibility criteria	✓	✓							
Written informed consent		✓							
Demographic data, medical history		✓							
Questionnaires (KDQoL, EQ-5D, PSQI, SONG-HD) and TTR		✓	✓		✓			✓	
Questionnaire (MoCA)		✓			✓			✓	
Participant self-completed baseline health economics questionnaire		✓							
Participant self-completed resource use/expenditure questionnaire and diary			✓		✓			✓	
Randomisation		✓							
Urine collection		✓						✓	
Residual kidney function (serum beta 2-M)		✓	✓*	✓*	✓*	✓*	✓*	✓	
Capture of routine clinical data		✓^	✓^	✓^	✓^	✓^	✓^	✓^	
Capture of routine clinical data and resource usage (UKRR, SRR, HES, ONS, ISD)									✓
Cardiac MRI scan		✓♦						✓♦	
Pre and post dialysis blood test		✓♦						✓♦	

* Represents research blood samples drawn at the same time as routine clinical testing

^ Represents routinely collected data on all dialysis units. Data includes (i) adherence to the intervention (number of sessions attended and number of minutes); (ii) haemodynamics (ultrafiltration volume and pre-dialysis blood pressure), monthly blood results (urea reduction ratio, Kt/V, haemoglobin [incl. ESA prescription], ferritin and calcium/phosphate/pth) will all be recorded from the same dialysis session as the collection of routine monthly bloods, using the e-CRF. ♦

Represents participants recruited to the CMR sub-study only – limited sites participating.

Abbreviations: PSQI = Pittsburgh Sleep Quality Index; MoCA = Montreal Cognitive Assessment; UKRR = UK Renal Registry; HES = Hospital Episode Statistics; ONS = Office for National Statistics; ISD = Information Services Division; SRR = Scottish Renal Registry; CMR = cardiac magnetic resonance imaging.

10.3 Randomisation

Randomisation will be performed by the delegated research nurse/enrolling physician using a validated web-based system (Sealed Envelope Ltd) provided and managed through LCTU. Eligible participants will be randomly assigned in a 1:1 ratio to one of two arms:

GROUP A: extended hours nocturnal haemodialysis (6-8 hours of in-centre haemodialysis delivered overnight, 3 times per week for 6-months)

OR

GROUP B: daytime haemodialysis (3.5-5 hours of in-centre haemodialysis, 3 times per week during the day for 6-months).

For Group A, the timeframe from randomisation to commencing extended hours nocturnal haemodialysis will be **2 weeks**. Instances where this timeframe is exceeded will be reported as protocol deviations.

A random element has also been introduced to the minimisation algorithm so recruiters cannot predict the allocation with any degree of accuracy.), patients will be allocated using minimisation on stratification factors including haemodialysis unit and age (<65 years, ≥65 years).

Each participant will be given a unique participant ID number at randomisation. This participant ID number will be used to identify the individual participant throughout the study and will not be re-assigned to any other participant. Due to the nature of the intervention, blinding of the participants and the study team to the randomisation arm is not possible.

10.4 Internal pilot

10.4.1 Recruitment and retention

During the first 12 months of the recruitment period we will assess the feasibility of completing the study in the desired time frame using an internal pilot. Based on our experience, we will target the following:

a) Recruit a minimum of 2 new units per quarter; 8 units initiated at 12-months
b) Randomise an average of 12 patients per unit in the first quarter (i.e. 6 patients will start in-centre nocturnal dialysis); 96 participants randomised at 12-months
c) Experience a maximum 25% drop out rate in the first two weeks of starting in patients randomised to in-centre nocturnal dialysis; participant drop out in first 2 weeks of nocturnal dialysis is <25% at 12-months
d) Encounter a dropout rate of no more than 15% across the two study arms as a result of death, kidney transplantation and other factors (e.g. moving out of area); remaining loss to follow-up is <15% at 12 months

10.4.2 Stop-go criteria

A standard traffic light system will be implemented to assess progression to the full study based on the number of sites open to recruitment, the number of participants randomised and the completion rate.

The completion rate will be calculated as the number of participants who 'complete the study' after 6 months of intervention as a proportion of those randomised. Study 'non-completers' are defined as:

a) participants who do not adhere to the allocated intervention i.e. switching from intervention to control in the first 2 weeks following randomisation (expected to be 25% of intervention participants) and

b) fail to provide 6 month follow-up assessment of KDQoL outcome (expected to be 15% due to loss to follow-up, transplant and death).

The target completion rate is 95% of the expected study completion i.e. at least 68.9% of randomised patients complete (0.95*(1-(0.15+(0.5*0.25))))

If we were to achieve 75% of the expected study completion i.e. 54.4% of randomised patients complete (0.75*(1-(0.15+(0.5*0.25)))) , the power of the primary outcome analysis would fall to 80%.

Progression criteria will be assessed by the DSMC at 12-months. The proposed length of the internal pilot phase is 12 months.

Table 2: *Internal pilot progression criteria*

Progression criteria	Red (stop)	Amber (amend)	Green (go)
Study recruitment	<75%	75-94%	=95%
Recruitment rate/site/month	<1	1	>1
Number of sites opened	≤5	5-6	8
Total number of participants recruited	71	72-95	96
Study completion rate	<54.4%	54.5-68.8%	>68.9%

- **Green criteria** = proceed to the main study (95% [minimum] of all targets reached)
- **Amber criteria** = discussion about what changes should be made (75% [minimum] of all targets reached)
- **Red criteria** = discussion with the option to stop the study (<75% of any target reached)

10.5 Embedded process evaluation (workstream 2)

10.5.1 Design

A process evaluation (over months 6-48) will provide formative evaluation of the study processes and activities, in order to refine and amend where needed, and an evaluation of the intervention's implementation, including: assessment of whether and how well implementation is per protocol (components, timing and duration etc.) and identification of the contextual factors that influence its implementation and adoption. Mixed methods will be used: collection and monitoring of quantitative data (much of which is already collected for the main study) and a mixture of ethnographic methods (observations, interviews and document collation) will be used to generate qualitative data.

We anticipate undertaking observations in, and collating documentation from, approximately half the total number of sites (n=9); typically, 2-3 visits per site at different time-points (e.g. pre-intervention, during the training period and during INHD delivery). Observations of usual care during a site's preintervention and of staff training will begin from month 7 onwards; observations during INHD delivery may be undertaken up until month 48. We will purposively sample participating units to reach a range in terms of NHS (hospital vs. satellite unit), commercial unit (3 providers), size of unit and socioeconomic characteristics of the catchment area – and start month (to allow spacing out of site visits).

Interviews will typically be triggered by observations – for example, interviewing staff that the researcher encounters/has an informal conversation with during an observation. Within the sample, we will seek to reach a range. Sampling of staff and patients for recorded interviews will depend on the size of the dialysis unit and will be continually reviewed by the Research Associate and team, in order to achieve a balanced sample in terms of demographics (patients/visitors) and role (staff). We anticipate sampling 20-40 patients

and 20-40 members of staff, but will regularly review this through ongoing analysis alongside data collection.

10.5.2 Process evaluation focus: implementation and adoption of intervention

a) **Usual care:** Prior to implementation, we will gather a picture of 'usual care' by undertaking observations of a small sample of dialysis units during daytime dialysis and conducting a small sample of interviews with staff and patients. Two types of haemodialysis centres are involved in the main study: those where INHD has already been implemented and those with no prior experience of in-centre nocturnal dialysis. The majority of data gathered on 'usual care' will be in the latter. Observations will focus on 'typical' practice, from preparation for the arrival of patients to recovery time from their dialysis session. A staff questionnaire to inform the health economic evaluation will also be embedded in this workstream. The questionnaire will be completed by a senior nurse responsible for the haemodialysis unit.

b) **Staff training and preparation:** In order to assess the feasibility, acceptability and staff's engagement with training, we will conduct observations of a sample of site initiation and set-up visits, as well as other relevant training and preparation activities. Formative feedback from our observations will enable rapid amendment and refinement of such activities in subsequent sites.

c) **Intervention element: 'starter pack':** As mentioned above, ongoing evaluation of the nocturnal dialysis programme in Leicester has led to the adoption of nocturnal dialysis 'starter packs'. These are intended to be a key component of the study intervention and will serve as a means through which formative findings from the ethnographic work (specifically factors that influence implementation of in-centre nocturnal dialysis) may be addressed. Our evaluation of the 'starter packs' will include: observation of their implementation and adoption by staff and patients, collation of associated documentation (e.g. photographs of objects/posters, **not** people) and a small number of interviews with staff/patients (as deemed appropriate and useful). This early evaluation will serve as a means through which formative findings (specifically factors that influence implementation of in-centre nocturnal dialysis) may be addressed. This may aid recruitment and retention during the study and help to bridge the second translational gap of implantation into practice.

The starter packs will continue to focus on three categories of factor:

- Patient level (e.g. blindfolds / earplugs to help sleep) [Leicester will provide the packs to sites for distribution at no extra cost].
- Unit level (e.g. recommending soft close bins to minimise disruption)
- Institutional level (e.g. provision of templates for business plans, staffing rotas and transport schedules)

As part of the ethnographic work to study INHD implementation (below), we will focus on 'starter pack' activities where implemented to date and use our findings to feed into suggestions of further starter pack activities.

d) **Intervention element: delivery and receipt of in-centre nocturnal dialysis:** As indicated above, we will use a combination of ethnographic methods to our study of in-centre nocturnal dialysis implementation and the contextual factors that influence this; this will include: observations in dialysis units overnight, informal (non-recorded) interviews (staff) during observations, collation of relevant documentation, and recorded interviews with staff and patients. We will focus on how in-centre nocturnal dialysis happens – from preparation for patients' arrival, through to their departure after dialysis, observing how the whole process mirrors and differs from daytime dialysis. We will observe whether it happens as planned or differs from protocol, and the factors

that influence this. Interviews will enable further exploration of issues that are observed from the staff and patient perspective. The health economic staff questionnaire will again be completed by a senior nurse responsible for the haemodialysis unit to understand how staffing and equipment differ from usual care.

10.5.3 Process evaluation schedule, recruitment and consent

We anticipate undertaking observations in, and collating documentation from, approximately half the total number of sites (n=9). The Nightlife study team and researcher undertaking the process evaluation will liaise with the site PI and unit manager to identify the date/time of observation periods.
In the lead up to the study (before observations begin) a researcher will visit each site and explain what will be involved in the process evaluation (observations, document collation and interviews); this will give staff the chance to ask questions about the study and express any concerns.

a) Observations

Although staff and patients or visitors being observed will not be formally recruited to the study, we will seek to ensure that all staff and patients or visitors present during planned observation periods are fully informed about the study. Written consent will not be obtained prior to undertaking observations. We will therefore apply under section 10 of the Confidentiality Advisory Group (CAG) precedent set review pathway as there may be a risk that the observer is exposed to disclosure of confidential information. Information sheets will be provided for both staff and patients in an area of the dialysis unit accessible to all. During observations the researcher will always explain who they are and will wear an appropriate identifying badge. On observation days, posters will be displayed explaining that if staff, patients or their visitors ask the researcher to leave for any reason, then they will withdraw straight away.

Although the nature of the observations mean that it will not be possible to obtain written consent from individuals, the researcher will obtain verbal permission (sometimes this may be from the ward manager on behalf of others) to conduct observations on the unit overall. The researcher will ask the ward manager to circulate an email to staff to inform them before observations take place, along with a copy of the participant information sheet. Then, for observing in each area of the unit, a member of the clinical team (who by default, may also be a member of the research team) will seek verbal permission from the patients present. The researcher will obtain a letter of access from each of the Trusts prior to working on the dialysis unit. Staff and patients will have the right to refuse to be observed if they wish. Permissions and refusals will be documented by the researcher, however no identifiable data will be collected. Each observation period will last approximately 6-8 hours, for example, to include a nightshift and handovers.

For staff/patients who are not invited to a subsequent interview, their participation ceases at the end of the observation period that they were included in. All, however, will be informed that they can withdraw their data at any point and how to access the study findings.

Observations will not be digitally recorded; they will be 'recorded' in the form of anonymised notes in a notebook. An encrypted digital voice recorder will be used to record the researcher's reflections; this will always be conducted in a private area and after the observation has taken place.

b) Interviews

Eligible staff/patients will be approached by a member of the clinical team (who by default, may also be a member of the research team) and invited to take part in a semi-structured interview. For patients, this is most likely to happen in person towards the end of an observation period, but may happen earlier in the observation. For staff, if this is not possible (for example, if a member of staff is too busy or has finished their shift), the researcher will ask the ward manager/site PI to pass on the PIS and consent form.

Those interested in taking part will be provided with an information sheet and consent form. The same study materials will also be left in an area of the unit that is accessible to all, meaning that staff and patients can contact the research team directly. When a participant has indicated willingness to be interviewed,

the researcher will arrange a convenient time and location to conduct the interview. Where possible, potential interviewees will be given at least 24 hours to decide whether to take part or not. However, our previous work indicates that this may not always be easy to achieve at a busy site. If it is more acceptable to staff and is less disruptive to their work, that we interview them then and there, we will do so. Because of the low risk nature of this aspect (interviews) we believe that this approach is justified.

The researcher will have received appropriate training in obtaining consent and have been delegated this task by the PI. Before proceeding, they will check that the interviewee has understood the information, has had opportunity to ask questions and has capacity. The researcher will obtain consent immediately prior to the interview: written informed consent will be obtained for face-to-face interviews. All consent forms will be retained at sites. In addition, verbal consent will also be obtained and recorded on an encrypted digital recorder for telephone interviews at the start of each recording.

A participant's involvement in the study ends once the interview is complete.

Participants can withdraw their data up to 4 weeks after the interview. Their data will be pseudonymised after 4 weeks and therefore it will not be possible to identify who a transcript belongs to. Participants wishing to withdraw within the 4 weeks following their interview should contact the researcher who will identify what data is held and where and arrange for the data to be destroyed. This should be recorded and stored with the participant's consent form.

a) Virtual semi-structured interviews and virtual photovoice

An alternative method of qualitative data collection has been introduced to add resilience to the study in the COVID-19 era, thus making the deliverability of the process evaluation (workstream 2) more robust. The following strategy is proposed – a virtual, two-step, qualitative, exploration of usual care. This will assist the researcher to gain an understanding of usual haemodialysis practice and the patient experience of this where observational research cannot take place due to COVID-19 restrictions, but will also continue to be a flexible option for staff members and patients going forward. An electronic consent process has also been introduced to add resilience where face-to-face consent is not feasible.

(i) Semi-structured, virtual interviews with staff

- Eligible staff will be approached by a member of the clinical team and invited to take part in a semi-structured virtual interview. Posters and information leaflets advertising the study will be displayed in an area of the dialysis unit that is accessible to all, meaning that staff can contact the researcher directly.
- When a staff member has contacted the researcher to confirm their interest in taking part, the researcher will ask the staff member for their email address in order to email them a copy of the PIS if they haven't already obtained one at their dialysis unit. They will then arrange a convenient time to discuss the study and complete the electronic consent process*.
- Staff interviews will be done virtually (e.g. via Skype, MS Teams, Zoom or Google Hangouts) and will take place prior to virtual photovoice with patients so the researcher can gain an understanding of the practices and procedures at dialysis units, as well as staff roles.
- Questions will be based on the existing topic guide for workstream 2, with additional questions around the impact of COVID-19 on observational research.
- As well as including questions from the topic guides, the researcher will draw a map of the staff member's description of usual care and share it with them at the end of the interview to confirm authenticity. This will create a bank of visual images of usual care that can be viewed together to gain an appreciation of standard practice across the participating sites.
- In keeping with the face-to-face interviews, it is expected the virtual interviews will last no longer than one hour.
- Virtual interviews will be audio-recorded and transcribed anonymously, as per section 10.5.4.

(ii) Virtual photovoice with patients

- Eligible patients will be approached by a member of the clinical team and invited to take part in virtual photovoice. Posters and information sheets advertising the study will also be displayed in an area of the dialysis unit that is accessible to all, meaning that patients can contact the researcher directly.
- Virtual photovoice will take place after the staff interviews so that the researcher can explore how the patient fits into the detail provided by staff, and to explore the patient experience of this.
- Once the patient has contacted the researcher to confirm their interest in taking part, the researcher will ask the patient for their email address in order to email them a copy of the PIS if they haven't already obtained one at their dialysis unit. They will arrange a convenient time to discuss the purpose of photovoice and the ethics of taking photographs (e.g. no photos directly showing faces or identifiable details, asking permission to take photos in public places, etc.). There is published best practice guidance which the researcher can refer to (59). The electronic consent process will also be completed during this time*.
- Due to ethical and COVID-19 considerations, patients will be asked to use their personal smartphone and download the WhatsApp app. A study-specific smartphone can be loaned to patients who do not own a smartphone to ensure inclusivity. Email will be offered as a flexible alternative if patients do not wish to use WhatsApp.
- The researcher will have access to a study-specific smartphone for the purposes of virtual photovoice. When not in use, it will be stored in a locked drawer in the researcher's office at the University of Leicester.
- An agreed time period (usually one week, but allowing flexibility for patient preferences) to take photographs of anything that shows their experience of haemodialysis. The researcher will encourage patients to take photographs that show their emotional experience as well as their practical experience.
- The researcher will set up individual WhatsApp conversations and patients will be asked to send each photograph after taking it via this WhatsApp conversation (or via email if not using WhatsApp). The researcher will respond as soon as possible and engage the patient in a quick text conversation about the image and ask questions based on the SHOWeD framework (60). This process will continue throughout the virtual photovoice phase of workstream 2.
- After the one week period, the researcher will arrange a convenient time to interview the patient to discuss their photographs as a whole. This will be done virtually, (e.g. via Skype, MS Teams, Zoom or Google Hangouts) and can be while the patient is on dialysis, either using their own device or a device loaned by the researcher. The photographs and subsequent discussions about them will help the researcher to better understand the experience and practice of dialysis.
- The final interview with patients will be audio-recorded and transcribed, and findings will be analysed using a specific photovoice analysis method called interpretive engagement (61) and NVivo.
- In line with the timeframes for interview audio-recordings, WhatsApp conversations will be retained for 4 weeks, after which point they will be deleted following pseudonymisation.
- All photographs shared will be uploaded to the researcher's University of Leicester encrypted laptop under password-protected conditions and stored securely on the R:Drive. Photographs will be stored in a secure location for at least 15 years after completion of the study.

(iii) * Electronic consent using DocuSign

For both virtual semi-structured interviews with staff and virtual photovoice with patients, a simple electronic consent platform (DocuSign) will be used where face-to-face consent is not feasible. This model will allow for a resilient response to local lockdowns as well as mitigate for the ongoing impact of COVID19 and the potential of further waves. DocuSign has demonstrated compliance with government regulations and frameworks that were developed to ensure the privacy and security of personal and sensitive confidential information, including GDPR and ISO 27001:2013 (highest level of certification available for

global information security). In addition, DocuSign has received EU commission approval for its Binding Corporate Rules (BCR), widely considered the gold standard for data protection.

Step-by-step outline of electronic consent process:

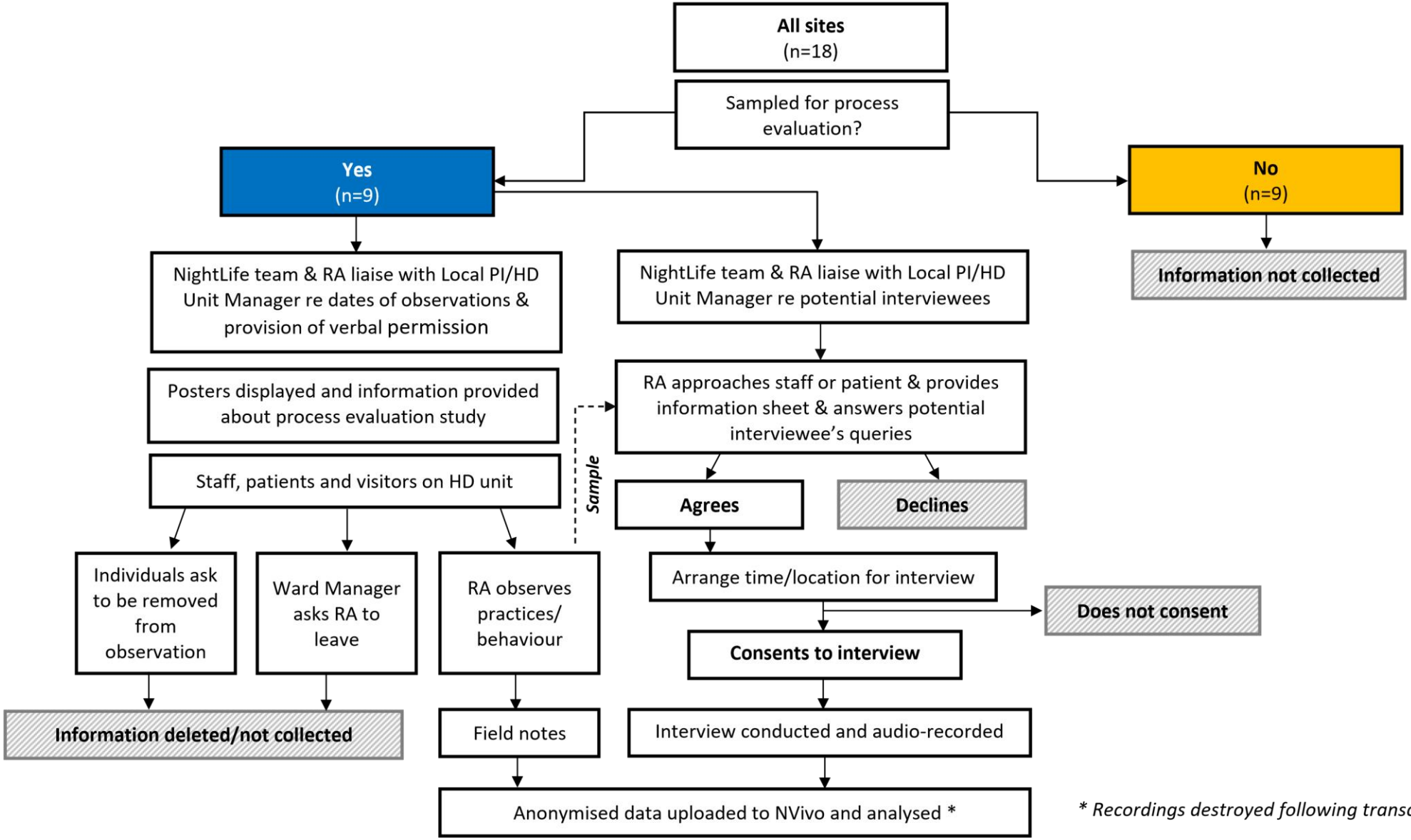
- Potential participants will contact the researcher directly to express an interest in partaking in the virtual semi-structured interviews/virtual photovoice.
- The researcher will obtain the staff member/patient's email address for the purposes of electronic consent and emailing a copy of the PIS, and will arrange a virtual consent discussion.
- Once the participant has reaffirmed their decision to take part, electronic consent will be obtained in real-time during the virtual consent discussion using DocuSign. The consent process will be supported either over the telephone or by videoconference to confirm the participant has understood the PIS and has had any questions answered satisfactorily.
- The researcher will log into the DocuSign portal, select the relevant consent form (i.e. staff or patient) and enter the relevant details (i.e. names and email addresses). The consent form will be automatically emailed to the participant for signing using the details entered by the researcher. The electronic consent form will mirror the content of the paper documents.
- The participant will be asked to access their email account in order to open the electronic consent form. There will be placeholders within the electronic consent form which will guide the participant in terms of where to initial for mandatory clauses and where to tick yes or no for optional clauses. The participant will then sign electronically and click 'finish'.
- Once the participant has clicked finish, the partially signed consent form will be automatically returned to the researcher via email.
- The researcher will review the consent form, add their name, signature, date and click 'finish'.
- Once both parties have signed the consent form, they will automatically receive a fully signed PDF copy via email for their records.
- The DocuSign portal will only be accessible by the researcher who will maintain an anonymised consent log for monitoring and auditing purposes. Completed consent forms will be stored electronically on the secure R:Drive.

10.5.4 Process evaluation analysis

The researcher will take anonymised field notes (typically handwritten in a notebook) while observing the practices and behaviour of staff and patients and including informal discussions, focusing on the starter packs and INHD. The researcher will keep the notebook on their person at all times while on the dialysis unit. As soon as feasible after leaving the dialysis unit, the researcher will either a) type up the anonymised notes into a word document or b) dictate the notes into an encrypted digital recorder, the recording of which will be sent securely to be transcribed into a word document. All resulting word documents (and NVivo software files used for analysis) will be kept on a secure University of Leicester drive and anonymised copies of key documents for analysis will be stored on a secure University of Edinburgh drive by the workstream 2 lead. The researcher will also collate relevant documentation for further context and insight. The researcher will audio-record post-observation 'debriefs' either alone or through discussion with the qualitative lead. Field notes and debriefs will be fully transcribed. Interviews will also be audiorecorded and fully transcribed by the researcher. Once the data has been uploaded to NVivo qualitative data indexing software, recordings will be destroyed.

Analysis will be informed methodologically by constant comparative approach (47) and theoretically by Normalisation Process Theory (48) and New Materialism (62). The iterative and ongoing concurrent nature of data collection and analysis the internal pilot means that rapid formative feedback can be provided to continuously refine components of the intervention, specifically the 'starter packs' to enhance adoption of the intervention and maximise participation and adherence to the study and intervention.

Figure 3: Process evaluation schedule, recruitment and consent flow chart



** Recordings destroyed following transcription*

10.6 QuinteT Recruitment Intervention (QRI) (workstream 3)

Two key recruitment concerns were raised through the PPIE/staff discussions in the lead up to the grant application: (i) the potential for 'resentful demoralisation' in patients allocated to the control group, and (ii) the possibility that clinicians would consciously or sub-consciously discuss the study with select patients, rather than the full spectrum of eligible patients. We plan to mitigate and address these issues through an integrated QRI to optimise recruitment processes. This will seek to understand the factors influencing recruitment and retention in 'real-time', and then use these insights to inform interventions designed to improve recruitment processes for the remainder of the study. The overall aim of this work is to ensure all eligible patients receive full, clear, and accurate information about the study, to enable an informed decision about participation. This will be achieved by: a) identifying, understanding, and addressing equipoise issues amongst clinicians, and b) gaining a better understanding of how the study is communicated to/understood by patients. We intend to reduce the risk of resentful demoralisation and crossovers by helping patients to understand the potential advantages/disadvantages of both study arms.

This will be achieved by employing QRI methodology: a mixed-methods approach that has been implemented in over 30 RCTs to optimise recruitment and informed consent (52). The QRI employs qualitative and mixed-method approaches to understand recruitment issues rapidly (Phase 1), and then uses this evidence to design and implement tailored strategies to optimise recruitment processes (Phase 2). This work package will complement and build upon the component of the internal pilot and process evaluation which involves monitoring recruitment and retention. Further information on Phase 1 and Phase 2 can be found below.

10.6.1 Phase 1: Understanding recruitment

Phase I aims to understand study recruitment processes and how these may differ across participating sites. A multi-faceted, flexible approach will be employed, including one or more of the following:

a) Semi-structured interviews with: (i) members of the TMG (n=5-10), (ii) clinicians or researchers involved in study recruitment ('recruiters') (n=10-25), and (iii) eligible patients who have been approached to take part in the study (n=5-15). Interviews with members of the TMG and recruiters will focus on: their perspectives on the evidence upon which the study is based; perceptions of uncertainty/equipoise; views on the appropriateness of eligibility criteria, and (where relevant) experiences of recruitment difficulties or successes. Interviews with patients will explore views on the presentation of study information, understandings of study processes (e.g. randomisation), and reasons underlying decisions to accept or decline the study. Patients will be purposefully sampled, to build a sample of maximum variation based on age, gender, study centre, and their decision about study participation (i.e. accept or decline). Interviews will be conducted via telephone or a secure web-conference facility (e.g. Skype, MS Teams, Zoom or Google Hangouts), where conducting these in person is not feasible.

b) Analysis of audio-recorded recruitment discussions: 'Recruitment consultations' between recruiters and potential participants will be audio-recorded with permission. This will be a core aspect of data collection, as it allows an opportunity to investigate actual (rather than perceived) recruitment behaviours. The audio recordings will be used to examine how the study treatments and study processes (e.g. randomisation) are explained to patients, how equipoise is conveyed, and how patients react to the information provided. Audio-recordings of recruiter-patient consultations do not require the presence of a researcher. The original protocol processes can be followed if recruitment consultations continue in person. If recruitment consultations need to be conducted remotely via telephone due to COVID-19 restrictions, equipment will be provided to allow the recruiters to audio-record their telephone calls with patients (upon receipt of appropriate consent).

c) Scrutiny of study screening logs and mapping of recruitment pathways: working in close collaboration with LCTU, we will design a comprehensive screening log to capture numbers of patients screened, eligible, approached, randomised, and numbers accepting their randomised allocation. The logs and interviews (described above) will be used to construct flow charts depicting the 'recruitment pathway' for each centre, and the points at which patients enter/exit the pathway. Numbers captured in the screening logs will be compared across centres and considered in relation to estimates specified in the grant application/study protocol. This process will be regularly repeated to identify bottlenecks in the recruitment pathway and inform further data collection through interviews and/or analysis of consultations.

d) Observation of TMG and Investigator meetings: TMG meetings will be regularly observed to gain an overview of study conduct and overarching challenges (logistical issues, etc.). The QRI researcher will take contextual notes, but meetings will not be audio-recorded, and no direct quotes will be used in research. TMG members' perspectives may be explored through the interviews discussed above.

10.6.2 Phase 2: Development and implementation of recruitment intervention strategies

Working closely with the CI and TMG, we will formulate a 'plan of action', consisting of specific strategies designed to improve recruitment and informed consent processes. The plan will be informed by Phase 1 evidence and is likely to include generic and site-specific interventions. Generic interventions may include written guidance documents that provide suggestions on how to explain the study to patients in a balanced way (i.e. conveying equipoise). Supportive feedback will feature heavily in the plan of action, with the precise nature and timing dependent on the issues that arise. For example, feedback may be offered to individual centres, through multi-centre feedback or confidentially to individual recruiters. All feedback will be supported with anonymised data extracts from interviews and recruitment consultations.

Although the QRI has been presented as two distinct phases for clarity, the phases will overlap. New avenues of enquiry will arise as data collection proceeds and new centres open, and the feedback sessions themselves may highlight new issues that warrant further investigation. Screening logs will be assessed throughout the recruitment period, with particular scrutiny of figures before/after Phase 2 interventions are implemented. This will help to inform decisions about further investigation or intervention throughout the study's recruitment period.

10.6.3 QRI consent processes

Healthcare professionals (HCPs) involved in the NightLife study recruitment will receive a copy of the 'QRI healthcare professional information sheet' at Site Initiation Visits (SIVs) or via email from the QRI researcher. This will explain the QRI processes described above (specifically, audio-recording of recruitment discussions and interviews). Informed consent will be obtained by the research nurses or the QRI researcher through a 'master' consent form, with individual statements pertaining to each research activity. HCPs may opt to participate in just one, both, or neither of the QRI elements.

Consent can be obtained in-person or remotely and either in writing or verbally. Where verbally, the research nurse or QRI researcher will read each statement on the consent form, initial these as is appropriate, and sign to confirm that the HCP has given consent. The consent discussion will be audiorecorded and a copy of the completed form will be given to the participant for their records. All QRI consent forms will be retained at sites.

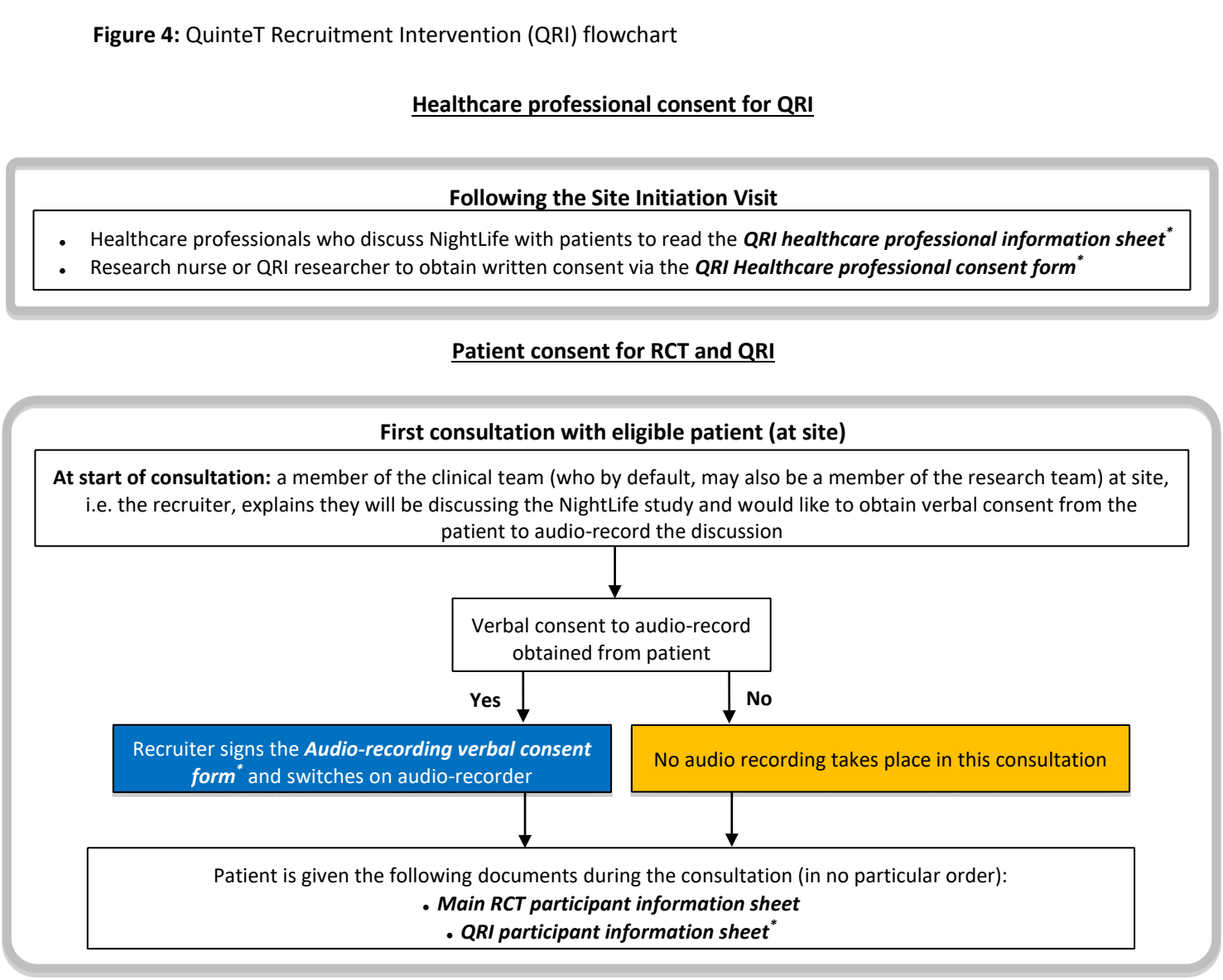
Patients will also receive a 'QRI patient information sheet' (PIS) explaining the audio-recording of recruitment discussions and the possibility of being approached for a future interview. The PIS will be handed to patients during the discussion about the RCT. As we wish to capture how the RCT is introduced

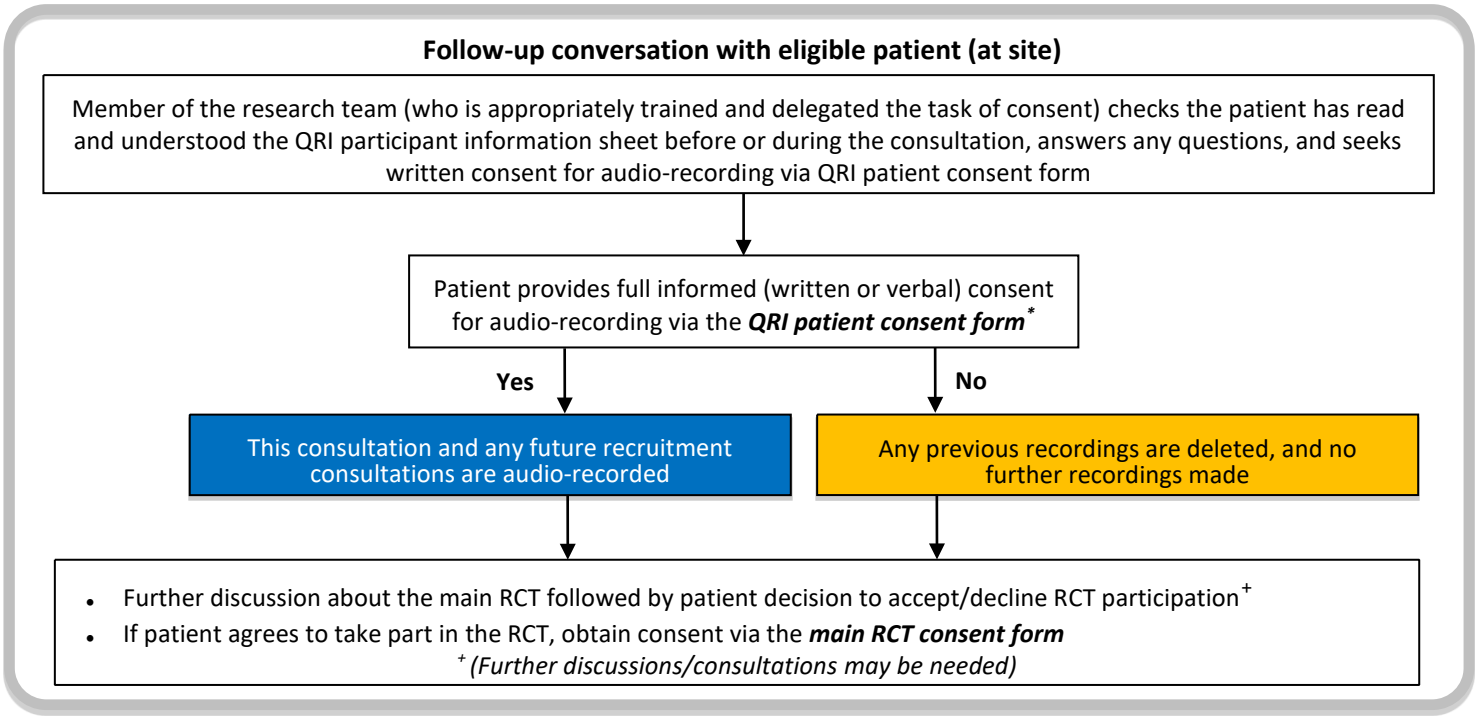
to patients, we will employ a two-step consent process for audio-recording recruitment discussions. This is depicted in the flow chart below (figure 4). In brief:

- A member of the clinical team (who by default, may also be a member of the research team) will obtain initial verbal consent to record the discussion about NightLife. If patients agree, the 'verbal consent form' will be signed by the HCP to document that verbal consent has been obtained, and the discussion will be recorded.
- Patients will receive the QRI PIS in the consultation, and will be provided sufficient time (typically at least 24 hours) to ask any questions and consider their participation in the QRI.
- Patients will be asked to provide full informed consent for the audio-recordings and/or interviews in person at their subsequent visit or remotely, whichever is most appropriate. Full informed consent can be obtained in writing or verbally. The verbal consent option can be employed irrespective of whether the encounter is taking place in person or remotely. Where the verbal option is employed, a member of the clinical team or research team (can be a different person to the one who obtained initial verbal consent) will read each statement on the consent form, initial these as is appropriate, and sign on the participant's behalf. The consent discussion will be audiorecorded and a copy of the completed form will be given to the participant for their records. All QRI consent forms will be retained at sites. Further RCT recruitment discussions will be audiorecorded subject to receiving full consent; if written consent is not obtained for audio-recording, the recording captured from the discussion will be deleted (if collected) and no further recordings made.

As per above, patients can accept or decline participation in the audio-recordings, interviews, or both. Their decision(s) about QRI participation will be independent to their decision about RCT participation.

Figure 4: QuinteT Recruitment Intervention (QRI) flowchart





** The QRI element has been labelled as the 'communication study' in all documentation to make it easier for participants to understand the different elements they may be involved in.*

10.6.4 QRI data analysis

All qualitative interviews will be audio-recorded using digital encrypted recorders, transcribed verbatim, and edited to ensure anonymity. Audio-recordings will be transcribed by internal University of Bristol staff or an external transcription company which has signed the necessary University of Bristol confidentiality agreements. Transcripts will be pseudo-anonymised. Interview data will be managed using NVivo software (QRS International) and analysed thematically using constant comparative approaches adopted from Grounded Theory (53). Audio-recorded recruitment consultations and follow up discussions will be subjected to content, thematic, and novel analytical approaches, such as targeted conversation analysis and appointment timing (the 'Q-Qat method')(54). There will be a focus on aspects of information provision that are unclear, disrupted, or potentially detrimental to recruitment and/or adherence. Standard approaches to enhancing rigour, such as double-coding, triangulating, and seeking out 'negative cases', will be employed throughout. A detailed description of how the QRI methodology achieves rapid analysis whilst maintaining rigour is detailed elsewhere (50).

10.7 Health economic evaluation

Renal replacement therapy (dialysis and transplantation) is needed by 64,000 people in the UK alone and has a high cost, consuming 1-2% of the NHS budget (57). These high costs necessitate complex economic modelling of renal interventions which alter quality of life, clinical outcomes, dialysis setting and cost, both within and beyond the study. There are no existing health economic evaluations of nocturnal in-centre dialysis but the initiation and continued support of nocturnal dialysis programmes requires institutional support from dialysis providers; providing evidence that such schemes are cost-effective is therefore crucial (6).

10.7.1 Data sources

Resource use, expenditure data and broader social data will be collected from a participant self-completed questionnaire at baseline, 1-, 3- and 6-months as well as routine clinical databases (HES, ONS and UKRR). To minimise recall bias, participants will be issued with diaries in which to record their healthcare visits and other related resource use and expenditure to aid completion of the aforementioned self-completed

questionnaire. Data collected will include healthcare-related costs (i.e. hospital admissions and length of stay, visits to and from healthcare professionals, medication) and patient- and carer-borne costs, earnings and savings (i.e. changes in employment, leisure activities and unpaid care of others due to dialysis, associated travel and intercurrent illness). Resource use data will be combined with unit costs using standard validated tools to obtain a cost per patient. To validate the healthcare resource use and expenditure data collected from patients, responses for a sample of participants will be compared to routine clinical data from healthcare secondary care records. We will obtain data on set-up and ongoing staff and resource costs from a subset of participating sites. A staff questionnaire to inform the health economic evaluation will be completed by a senior nurse responsible for the haemodialysis unit before and after implementation of the intervention. This will help us to understand how staffing and equipment differ between usual care and in-centre nocturnal dialysis.

Quality Adjusted Life Year (QALY) will be derived using the EQ-5D data collected from patients at baseline and 1-, 3- and 6- months. These measures will be combined with health-related quality of life index scores based on surveys from the UK population using established methods to generate QALY profiles.

10.7.2 Within study analysis

The difference in resource use, costs and quality of life adjusted life years between the intervention and control arms will be calculated. An intention to treat and per-protocol analysis will be performed (the latter informing the beyond study model below). This will reflect set-up and per session costs, ultimately reporting the cost per QALY gained; that is, the ratio of the change in costs to the change in QALYs between the two groups. The incremental cost per dialysis treatment and cost per patient per year will also be calculated. A sensitivity analysis will be undertaken to assess the robustness of the results to any assumptions made in the analysis.

10.7.3 Beyond study modelling

We will use a probabilistic state transition decision model to project costs and effects over the longer term. The model structure will be developed in conjunction with clinical experts as well as informed by the literature and the health states included states will reflect standard in-centre HD, nocturnal long hours, home haemodialysis, kidney transplantation and death. Patient level characteristics will inform the probabilities of moving between these states. These characteristics and probabilities will be informed by our within study analyses and other information sources. This allows us to reflect any association between the intervention and a how a preferable cardiovascular phenotype associated with the intervention which has both improved survival on dialysis and fitness for kidney transplantation and the survival this modality brings. Health related quality of life Quality Adjusted Life Year (QALY) will be estimated by extrapolating the QALY profiles calculated within the study to the longer term. This extrapolation will be informed by the literature, clinical experts and external data sources.

10.8 NightLife-CMR: Cardiac MRI sub-study (appendix 2)

A separately funded CMR sub-study (British Heart Foundation, ref PG/20/10132) will take place in a selection of sites participating in the main NightLife RCT. The sub-study will assess whether dialysing over a longer period of time (6-8 hours) overnight reduces levels of myocardial fibrosis (measured with MRI) compared to staying on conventional haemodialysis. Please refer to appendix 2 for further information.

10.9 Withdrawal criteria

Participants may withdraw from (a) complying with the allocated study treatment and/or (b) providing data to the study, at any time for any reason without affecting their usual care. Should a participant wish to withdraw from receiving their allocated study treatment, efforts will be made to continue to obtain follow-up data, with their permission. Participants do not have to give a reason for withdrawal, however if they do provide a reason for leaving the study, this will be documented in the e-CRF. Any data collected until this point will be retained, analysed and used in the final analysis. If participants allocated to nocturnal haemodialysis revert back to daytime dialysis, they will still be approached to complete the questionnaires

unless they specifically withdraw consent. In addition, the Investigator may discontinue a participant from the study at any time if considered necessary. Projected dropout of participants is accounted for in the sample size calculation and therefore withdrawn participants will not be replaced.

It is likely that some data may not be available due to death, kidney transplantation, and voluntary withdrawal of patients or lack of completion of individual data items. Where possible the reasons for missing data will be ascertained and reported. Although every effort will be made to minimise crossovers from both intervention arms, the numbers, direction and reasons for participants moving between arms will be recorded and reported in line with CONSORT (Consolidated Standards of Reporting Trials) guidance.

10.10 End of study

End of study will be defined as the collection of 3 year outcome data from the last participant. Direct involvement of participants in the study will end after their completion of the 6-month intervention.

10.11 Follow-up

Follow-up information will be co-ordinated with routine dialysis appointments as participants will already be attending hospital and satellite haemodialysis centres on a weekly basis. Participant follow-up will comprise:

a) Questionnaires (KDQoL, EQ-5D, PSQI, SONG-HD) at one, three and six months
b) Participant self-reported resource use and expenditure questionnaire and diary at one, three and six months
c) Residual kidney function: urine collection at baseline and 6-months and serum beta 2-M at baseline and monthly thereafter throughout the 6-month intervention period (drawn at the same time as routine clinical testing)

d) Capture of routine clinical data and resource usage (UKRR, HES, ONS and ISD) on the three year anniversary of the last participant last visit (to ensure that there is at least 3 years' follow-up data for every participant).

10.12 Compliance with study protocol

This study will use the published definition of compliance of having attended 80% of appointments of randomised type (irrespective of length).

Statistical analysis will explore patterns of compliance using the following data:

- Number of day sessions undertaken;
- Number of sessions where fewer hours than defined for nights were taken;
- Missed appointments (for both night-time and daytime participants).

The study team will monitor and review protocol compliance and deviations from the protocol will be captured both within the source data and the LCTU Quality Management System. A protocol deviation is defined as any un-intended change or departure from the protocol which does not result in harm to the study participants or significantly affect the scientific value of the study. Minor deviations can occur frequently during the course of the study. Visit window deviations or difficulty obtaining urine samples at specified times will be considered minor deviations as they do not have the potential to cause harm to the participant or impact the integrity of the study.

Major deviations are events that cause or could cause harm to participants or others or that affect the fidelity of the research. Where deviations frequently reoccur, this may meet the criteria for a Serious Breach of GCP and will be reported in line with Sponsor SOPs. For the purposes of this regulation, a 'serious breach' is a breach which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the participants of the study; or • The scientific value of the study

If a participant decides to change from the treatment to which they were allocated, they will be followedup and data collected as per the protocol until the end of the study. However, every effort will be made to minimise crossovers from both groups. It will be made clear to study participants and clinicians that it is important for the integrity of the study that everyone follows their allocated treatment and we will be conducting a separate investigation into the behaviour behind consent to limit non-adherence to allocated treatment. Although every effort will be made to minimise crossovers from both intervention arms, the numbers, direction and reasons for participants moving between arms will be recorded and reported in line with CONSORT guidance.

This study will incorporate an intention to treat (ITT) approach when analysing the primary outcome. Therefore, if a participant allocated to the intervention arm receives less than 6 hours or more than 8 hours of HD delivered overnight, this will be reported as a deviation. Likewise, if a participant allocated to daytime dialysis receives less than 3 hours or more than 5 hours of HD delivered during the day, this will be reported as a deviation. Please see section 12.5 for further information on ITT.

10.13 Loss to follow-up

Based on our experience, we expect to encounter a drop-out rate of no more than 15% across the two study arms as a result of death, kidney transplantation and other factors (e.g. moving out of area). However we recognise the potential for attrition bias due to the unequal number of patients completing the protocol in the intervention group and the possibility of resentful demoralisation. We have taken steps to mitigate this is a number of ways:

- Inflating the sample size to account for non-adherence and drop-outs at all stages
- Undertaking an analysis into the attitudes behind recruitment and equipoise
- Continuing to collect complete data for patients who revert to daytime dialysis, receive a kidney transplant and adopting an intention-to-treat analysis
- Using multiple imputation methods through regression models to predict the endpoint values of lost patients
- Evaluating and improving trial management (e.g. starter packs) through the embedded process evaluation

Participants who are lost to follow-up will be censored for time to event secondary outcomes at the time of last contact or set as missing for others but will continue to be followed up for vital status using HES, ONS and UKRR where consent has been obtained.

11. SERIOUS ADVERSE EVENT MONITORING

NightLife is not a clinical trial of an investigational medicinal product, therefore the usual monitoring of pharmacovigilance and associated terminology is not relevant.

11.1. Definitions

11.1.1 Adverse Event (AE)

Any untoward medical occurrence in a study participant which does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the study, whether or not considered related to the study.

11.1.2 Serious Adverse Event (SAE)

A serious adverse event or reaction 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, or
- Is a congenital anomaly/birth defect
- Other important medical events ◊

* *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.*

◊ *Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.*

11.2 Reporting procedures for Adverse Events

Common non-life-threatening symptoms such as constipation, diarrhoea, headache, etc. do not need to be reported for this study. Only Serious Adverse Events (SAEs) that meet the criteria in section 11.3 will be recorded. No other non-serious adverse events will be recorded.

11.3 Reporting procedures for Serious Adverse Events

It is expected that participants will experience a significant number of underlying health conditions and consequently an increased number of expected hospital admissions. Therefore only SAEs that are clearly related to the study intervention and of a serious nature will be subject to expedited reporting to the Sponsor. This will comprise:

- Issues around vascular access, i.e. needle dislodgement during dialysis, causing bleeding
- Events that occur as a direct result of changes to a participant's dialysis prescription, e.g. hypokalaemia or hypophosphataemia
- Anything else in the Investigator's opinion that is related and unexpected.

These SAEs must be reported using the Expedited SAE Report From and sent via email to the Sponsor (with the NightLife mailbox copied in) immediately and within 24 hours of the research team becoming aware of the event. Once all resulting queries have been resolved, the Sponsor will send an acknowledgement of

the closure of the SAE. All correspondence and signed SAE forms must be retained by sites within the Investigator Site File (ISF).

All other SAEs will be recorded using the SAE Log CRF, which will document SAE name/description, outcome, treatment, severity, expectedness and relatedness to the study intervention. SAE data will be recorded on the Macro database at regular intervals so that LCTU can generate up-to-date reports for the annual DSMC meetings. The DSMC will review the listings for clinical relevance and advise the TSC and Sponsor on the suitability of the continuance of the study following their review of the ongoing safety data and whether any further data should be collected or additional analyses undertaken.

In addition to the reporting above, the CI or delegate shall submit once a year throughout the study or on request, an Annual Report to the Research Ethics Committee (REC) which lists all SAEs that have occurred during the preceding 12 months.

12. STATISTICAL ASPECTS

12.1 Statistical analysis plan

A statistical analysis plan (SAP) will be prepared by the Trial Statistician and will contain full details of all statistical analyses. The SAP will be prepared and finalised before the primary analysis database lock. It will be agreed with the DSMC, TSC and study investigators before data lock and published in a study protocol paper. Any changes to the original SAP will be detailed along with the reason(s) for their change in subsequent SAPs. No formal stopping rules or interim analyses have been pre-defined, beyond the internal pilot.

12.2 Power calculations

The study is powered to detect a standardised difference of 0.26 in the KDQoL 36 total score between groups over 6-months (measured at 1, 3 and 6 months), adjusting for baseline KDQoL 36 total score with correlation coefficient of 0.725. To achieve 90% power and a type I error rate of 5%, 216 participants are required. This allows for an overall attrition rate of 15% across both arms (for death and transplantation).

12.3 Sample size and justification

The original sample size was estimated using the best available KDQoL data at the time of application. A total of 252 patients (126 per group) were needed for analysis of KDQoL physical component to detect a 5-point difference (in a score ranging 0-100) between groups at 6-months post randomisation, adjusting for the baseline measure with 90% power at the 5% significance level. This was based on data from previous studies in a similar population showing the mean score in our proposed study cohort to be 59.37 (SD 19.54) (28). We assumed a correlation between baseline and 6-month KDQoL of 0.78 (40). The proposal was to randomise a greater proportion to the nocturnal intervention arm (4:3) to overcome an anticipated switch back of those allocated to nights to ensure adequate power in a per protocol analysis and therefore the overall recruitment target was 350.

Publication of the PIVOTAL trial (63) provided an opportunity to update and clarify some of the assumptions in estimating the sample size previously. The PIVOTAL trial reported data on the KDQoL-36 total score (ranging 0-500), therefore the minimal clinically important difference (MCID) needed further consideration. We calculated the MCID based on the new estimate of the standard deviation from the PIVOTAL data (71.28) maintaining the same magnitude of the effect size by using the same standardised difference of 0.26. Furthermore, the PIVOTAL trial reported a correlation coefficient lower than our original estimation (0.725) which was also incorporated. Finally, in practice the trial has not observed to date participants 'switching' back to days having recruited from several sites in the first phase of recruitment and therefore the TSC agreed to revert to a conventional 1:1 randomisation.

Furthermore, we are currently undertaking methodological work through a funded PhD to investigate methods for accounting for missing primary outcome data (anticipated for and sample size inflated by 15%) as a result of death and transplantation. The analysis plan, in time, might therefore reflect new methods that become available which also has the potential to increase trial power.

12.4 Descriptive analysis

Data will be checked for outliers and missing values and validated using the defined score ranges for all outcome measures. Standard statistical summaries (e.g. medians and ranges or means and variances, dependent on the distribution of the outcome) will be calculated for baseline data to check comparability between treatment arms, and to highlight any characteristic differences. Statistical tests for imbalance will not be carried out. It is likely that some follow-up data may not be available due to death, kidney

transplantation, and voluntary withdrawal of patients or lack of completion of individual data items. Where possible the reasons for missing data will be ascertained and reported. Although every effort will

be made to minimise crossovers from both intervention arms, the numbers, direction and reasons for participants moving between arms will be recorded and reported in line with CONSORT guidance.

12.5 Analysis of primary outcome

The primary analysis will compare the KDQoL 36 total score over 6-months between the two groups. The primary analysis will be conducted using a modified intention to treat (ITT) with participants with at least one post baseline measurement of KDQoL analysed in the groups to which they were randomly allocated, regardless of what dialysis they actually received. The KDQoL SF-36 total score over 6 months (i.e. 1-, 3- and 6-months) will be compared between the treatment arms using a repeated measures mixed linear regression model with participant as a random effect to account for repeated measures over time. The model will be adjusted for a treatment group, minimisation factors (haemodialysis unit and age) with haemodialysis unit as a random effect, and baseline KDQoL 36 total score. Treatment comparison estimates will be presented as adjusted mean difference and 95% confidence intervals (95% CI). By design there will be no missing data for the minimisation factors, if the KDQoL 36 outcome is missing for less than 5% of the study population over 6 months, a complete case analysis will be conducted. If there is more than 5% of participants with a missing post baseline KDQoL score, multiple imputation will be used. The imputation will be carried out using the command MI in Stata. MI replaces missing values with multiple sets of simulated values to complete the data, performs standard analysis on each completed dataset, and adjusts the obtained parameter estimates for missing-data uncertainty using Rubin's rules to combine estimates.

12.6 Sensitivity analysis of the primary outcome

There is increasing demand by clinicians and patients for 'per-protocol' analyses which quantify the effect of being randomised to, receiving and continuing a treatment (45). A secondary, complier average causal effect analysis (CACE) analysis will be conducted to understand the efficacy of nocturnal dialysis in those that receive it as planned (i.e. participants without a protocol deviation stating their allocated intervention was not delivered as expected in the protocol)Clinical experience suggests that the development of new conditions which cause instability of the patient while they are on dialysis may mean that patients in the intervention arm will have to return to usual care during the day. We will assess the effect of such switching on the treatment effect found.

Subgroup analyses will be limited to the same variables used as minimisation variables. Tests for statistical heterogeneity (e.g. by including treatment group by subgroup interaction parameter in the regression model) will be performed prior to any examination of effect estimate within subgroups.

12.7 Analyses of secondary outcomes

The secondary outcomes will be analysed using linear regression for single point in time continuous outcome measures, repeated measures mixed linear regression model for secondary outcomes measured repeatedly over time and logistic regression for binary measures. All analyses will be adjusted for baseline value and the minimisation factors. The number of deaths and cardiovascular events expected is relatively low, therefore formal time to event analyses will not be conducted. Kaplan–Meier will be presented to describe the relationship between these events and treatment.

12.8 Analyses of serious adverse events

All serious adverse events will be tabulated and summarised by treatment group, according to system organ class and preferred term, as classified in the Medical Dictionary for Regulatory Activities (MedDRA). The version of MedDRA used will be specified within the SAP. No formal statistical testing will be performed. All events will be summarised by seriousness, expectedness and relatedness.

13. DATA MANAGEMENT

13.1 Data collection and source data identification

Source data will be collected prospectively on designated Case Report Forms (CRFs). The patient's medical notes will be a source for additional clinical data. Questionnaire data will be collected at baseline, 1-, 3- and 6-months during a routine dialysis session i.e. while the patient is attending their hospital or satellite unit, to minimise disruption and 'questionnaire fatigue'. Assessment of residual kidney function by measurement of urine will take place at baseline and 6-months. This usually happens following the end of the first dialysis session of the week and starts when the patient is asked to empty their bladder into the toilet when their dialysis is finished. They are then required to collect all the urine that they pass until their next dialysis session 2 days later (which often is not very much because of their kidney failure) and the test finishes when they collect any remaining urine on arrival at the dialysis unit. The results of the urine collection are matched to routine blood samples taken through the patients' dialysis needles at the end of the first dialysis session and the start of the second to give the measure of residual kidney function. An additional measure of residual kidney function (serum beta-2 microglobulin) is taken at the same time as the patients' routine monthly blood samples, again through the dialysis needles to make sure no additional venepuncture is required. These are outlined in table 1.

All missing data will be followed up and resolved where possible. If the item is not applicable to the individual case, N/A will be written. All entries will be printed legibly in black ink, following ICH-GCP guidelines. All CRFs will be stored in a secure area with restricted access. Each enrolled participant will be allocated a unique participant ID so that the CRFs and electronic database remains anonymous.

Copies of the participant consent form and information sheet will be provided to the participant and placed in the hospital notes of all participants and the original will be stored in the ISF. A sticker will be placed on the cover of the notes (or inside cover) for participants taking part in the RCT detailing the study title, contact details of the PI and the fact that the notes should not be destroyed for 15 years from the end of the study. All study visits summaries and SAEs will be recorded in the hospital notes.

Source data is defined as the first place data is recorded, this will include:

- Medical records
- CRFs
- Participant completed questionnaires and diaries
- Staff completed questionnaires
- Laboratory reports
- Printouts from equipment
- Field notes
- Audio-recordings

Audio recordings of clinical consultations taken as part of the QRI will be captured on encrypted audiorecording devices, which the QRI research team will provide to the site (with instructions). Recordings will be periodically transferred securely to the University of Bristol research team using a Trust-approved secure data transfer system (e.g. BOLT), or an encrypted device (e.g. password-protected flash drives or memory cards). The recordings will be transcribed and de-identified by a University of Bristol employee or a University of Bristol approved contracted transcribing service that has signed the University

of Bristol's Confidentiality Agreements. Transcripts and recordings will be held up to 10 years on a secure database at the University of Bristol which will only be accessed by authorised members of staff in the QuinteT team. For transcripts only, we will request separate permission for these to be stored indefinitely on a separate data repository (so other QuinteT researchers at the University of Bristol can apply for permission to access the transcripts for future ethically approved studies). Any paper copies of the transcripts will be stored securely in a locked filing cabinet at the University of Bristol and destroyed at the end of the NightLife study.
Digital recordings taken as part of the process evaluation will be stored on a secure University of Leicester server and will be deleted following transcription and anonymisation of the data. Recordings will be accessible only to essential personnel. All quotations or descriptions used in reports will be anonymised, and details may be altered to further protect anonymity. Field notes from observations will also be anonymised.

Both research teams will provide information on data storage to the central co-ordinating team at LCTU.

13.2 Data entry

Data entry will be conducted by the study delivery team at sites. Data collected from the source data as detailed above will be entered onto a validated web-based Remote Data Capture (RDC) system provided by the LCTU. Access to the e-CRF will be granted to authorised study personnel only via a secure password protected web-interface. The investigator and designated personnel must ensure accuracy, completeness and timeliness of data reported in the e-CRF and all required reports. Data reported on the e-CRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained.

On-entry validation checks will be applied where required, and data entered will be checked for completeness, accuracy and timeliness by the study team/study manager/data manager, with queries managed using the data clarification functionality within the clinical data management system (CDMS) system. A Data Management Plan will be created by LCTU with specific details on data handing and record keeping.

13.3 Data linkage

The investigators recognise the need to be efficient with their data collection procedures. Furthermore many augmented dialysis studies have demonstrated significant benefits to patients beyond the withinstudy period (43). Dialysis patients routinely generate granular data through a combination of the dialysis process, routine submissions to the UKRR for audit purposes, and through frequent hospitalisation and the associated diagnosis and procedure codes reflecting the associated activity.

13.3.1 Consent for data linkage

Building on the experience of large patient and centre level randomised trials (44), participants will consent for the investigatory team to link their research data to routine health data which will include UKRR, SRR, ONS, HES and ISD data. Consent will be sought from participants for their identifiable data (i.e.
NHS number, date of birth, gender and ethnicity) to be securely transferred from participating sites to the Sponsor institution and above data owners for subsequent linkage and return of associated patient data. On the three year anniversary of the last participant's last visit, linkage to determine longer term adherence to the intervention, mortality, modality changes, hospitalisation and associated reasons will be performed.

13.3.2 Data protection and participant confidentiality

Participants' personal data included in study-related databases shall be treated in confidence and in compliance with ICH-GCP, the UK Policy Framework for Health and Social Care and the EU General Data Protection Regulation (GDPR). When processing or archiving personal data, the Sponsor or its representative shall take all appropriate measures to safeguard and prevent access to this data by any unauthorised third party.

Each participant will be assigned a unique identification number upon recruitment. The database will be password protected and only researchers collecting data will have access to this database. All personalised information for participants will be kept confidentially at the recruiting site unless there is specific consent and HRA approval for transfer of this to another site for study-related purposes.

All electronic patient identifiable information will be held on a secure, password-protected database accessible only to essential personnel. Paper documentation will be stored in a locked filing cabinet in the relevant research office. Neither hard copies nor electronic files containing personal information will be removed from the research office or stored in a non-secure manner electronically. The study research team will comply with the Data Protection Policy of the collaborating Universities and local NHS Trusts. Direct access to source data / documents will be required for study-related monitoring. All paper and electronic data will be retained for at least 15 years after completion of the study.

Biological samples taken for the study will be destroyed once analysed in accordance with the Human Tissue Act 2004.

13.3.3 Data access and storage

Participating sites' source data, study documents, participant notes will be made available for monitoring, auditing and inspections by the appropriate regulatory authorities, the Sponsor, NHS host organisation and LCTU.

All study documentation will be retained in a secure location during the conduct of the study. Personal identifiable data will be retained by each participating site for a maximum of 12 months following the end of the study, after which it will be destroyed, unless participants have expressed an interest in being invited to the results dissemination event and/or receiving a copy of the study newsletter. In these circumstances, personal identifiable details such as names and contact details will be retained on a password protected database until required, and then destroyed.
All electronic data will be stored on secure network systems, to which only the relevant study personnel will have access.

For the purposes of this study, the University of Leicester will act as the Data Controller for data held on the CDMS. The University of Bristol will act as the Data Controller for data generated as part of the qualitative analysis. The University of Leicester will act as the data controller for the data held on the NVivo qualitative data indexing software as part of the process evaluation. NVivo transcription data is encrypted both in transit and at rest and only the account owner has access to and control over the data.

13.4 Archiving

Personal identifiable data generated by the study will be retained for the minimum time determined by the regulatory authorities following the notification of the end of the study before being destroyed in a confidential manner.

Following completion of the study data analysis, data and essential study records, including the final study report, will be archived in a secure location for at least 15 years after the completion of the study, in accordance with LCTU SOPs. The data will be archived at a Sponsor approved archiving facility which will

ensure that it is stored securely and accessed only by authorised individuals. No study-related records, including hospital medical notes, will be destroyed unless or until the Sponsor gives authorisation to do so.

14. STUDY ORGANISATION, REGULATION AND OVERSIGHT

14.1 Ethical and regulatory considerations

Once Sponsor authorisation has been confirmed, the protocol, informed consent form, PIS, interview topic guides and any proposed advertising material will be submitted to an appropriate REC, HRA, and host institution(s) for written approval. The study will commence once all relevant approvals are in place and Sponsor 'green light' for all sites to open has been issued.

Any subsequent amendments to the study's HRA approved documentation will require Sponsor, REC and HRA approval.

An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Otherwise, the Chief Investigator (or delegate) will notify the REC of the end of the study. Within one year after the end of the study, the Chief Investigator (or delegate) will submit a final report with the results, including any publications/abstracts, to the REC.

This study will be conducted according in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004) and the UK Policy Framework for Health and Social Care Research (2017). It will also be conducted according to ICH-GCP, relevant regulations and the SOPs and quality management procedures of Sponsor, host organisations and LCTU.

14.2 Assessment and management of risk

There are minimal risks associated with taking part in this study and participants will be made fully aware of any risks before consenting. All research investigations are detailed in the participant information sheet and will also be explained to the participant before each investigation to ensure that they are willing to undertake each one.

14.2.1 Potential risks and burdens to participants

- **Time commitment:** this is the main burden for participants in this study. We have minimised the impact for participants by making sure all the research visits/interactions can take place at an outpatient clinic (recruitment) or on the dialysis unit during their routine dialysis treatment (data collection). Any assessments that can be completed while participants are on dialysis (e.g. questionnaires) will be done so. Participants will be asked to fill in a series of questionnaires on four occasions, at the beginning, middle and end of the study. This will take about 30 minutes altogether. They will be administered whilst on dialysis so as to not require additional time when the patient would otherwise not be in hospital.

- **Risks associated with the intervention (extended dialysis):** we believe that having more dialysis is better for patient outcomes but, as with any treatment, changing the way in which it is delivered can have an impact on clinical parameters. For example, more phosphate is removed from the blood through the dialysis process if people have longer dialysis sessions. This is a recognised (and positive) benefit but does require regular review of a patient's prescribed medications (as many take tablets called phosphate binders to lower elevated phosphate levels) and sometimes even supplementation of phosphate in the dialysis fluid. We will reassure patients that their clinicians

will already be aware of this and that their dialysis prescription will be reviewed, as normal, during the routine monthly multi-disciplinary meetings.

- Participants who are randomised to nocturnal dialysis will be sleeping in dialysis units while undergoing treatment. It may therefore take them a while to adjust to sleeping through their treatment in an unfamiliar environment. There may be less opportunity to access additional resources face-to-face, e.g. doctors and dietitians, for those receiving nocturnal dialysis. However this will be replaced with telephone calls to ensure all participants receive the care they need. Dialysis prescriptions are also likely to change for those allocated to nocturnal dialysis. Participants allocated to nocturnal dialysis will continue to be reviewed on a monthly basis, including a review of their dialysis prescription, just as if they were receiving daytime dialysis.

Blood and urine samples: these samples are required to assess the effect (or not) of extended dialysis on a patient's residual kidney function. The blood test (beta-2 microglobulin) is not part of routine care but will be taken at the same time as insertion of the dialysis needles and drawing of routine monthly clinical blood tests. There will be no additional venepuncture required, nor visits to hospital. A urine specimen is also required at the start and end of the study; this has been discussed at length within the TMG, as well as with patient representatives, and although requires some time from patients, there is no risk to health.

14.2.2 Mitigation of potential sources of bias

- **Selection bias:** a web-based randomisation system (Sealed Envelope) will be used and a random element will be introduced to the minimisation algorithm so recruiters cannot predict the allocation with any degree of accuracy. Nevertheless, we acknowledge the possibility of selection bias as physicians may subconsciously (or deliberately) select patients to discuss trial enrolment from their dialysis patient cohort; this was highlighted in our PPIE/staff discussions.

- **Participant bias:** Resentful demoralisation was highlighted by our PPIE group as a real concern, that patients allocated to the control arm of the study may feel upset (potentially affecting the quality of life scores), drop out or switch allocation groups. In addition to offering control patients the opportunity to undertake nocturnal dialysis after completion of the study, our behavioural analysis will ensure that patients are properly consented and understand the importance of adherence to their allocated groups. Participating units will make every effort to continue to offer nocturnal dialysis as part of their clinical service so that patients may continue extended dialysis (or start if they were in the control group) once they have completed the protocol.

- **Attrition bias:** we recognise the potential for attrition bias due to the unequal number of patients completing the protocol in the intervention group and the possibility of resentful demoralisation. We have taken steps to mitigate this is a number of ways: (i) inflating the sample size to account for non-adherence and drop-outs at all stages; (ii) undertaking an analysis into the attitudes behind recruitment and equipoise; (iii) continuing to collect complete data for patients who revert to daytime dialysis, receive a kidney transplant and adopting an intention-to-treat analysis; (iv) using multiple imputation methods through regression models to predict the endpoint values of lost patients; and (v) evaluating and improving trial management (e.g. starter packs) through the embedded process evaluation.

14.2.3 Monitoring, audit and inspection

The University of Leicester, as Sponsor, operates a risk-based monitoring and audit programme, to which this study will be subject. The LCTU operates a Quality Management System, which will apply to this study with quality checks and quality assurance audits performed as required.

As part of the quality management process, the study will be subject to a risk assessment and a monitoring plan which will be developed by the Sponsor in conjunction with the CI and LCTU. The monitoring plan will consider the level of risk identified to participant safety, integrity of the study and study data validity and be informed by the UoL non-CTIMP trial risk based monitoring strategy to ensure the monitoring approach is targeted and justified. All study monitoring will be conducted in accordance with the monitoring plan

and will be undertaken by the study Sponsor or their delegate. All monitoring will be performed by staff who are ICH-GCP trained and are competent in monitoring to all applicable regulatory guidelines. A documented monitoring log and audit trail will be maintained throughout the lifetime of the study.

14.2.4 Study registration

The study will be registered on a recognised clinical trials database (ISRCTN registry) prior to recruitment commencing.

14.2.5 Insurance and indemnity

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

If a participant is harmed due to negligence, this will be covered by the local NHS Trust(s) indemnity arrangements for all participants in clinical trials. 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 participant information sheet.

14.2.6 Trial management

LCTU will be the coordinating centre for this study. It is a UKCRC registered clinical trials unit with extensive experience of running large multi-centre trials. LCTU has been involved in the development and design of the protocol since conception of this trial and will oversee quality assurance, trial management, data management and statistical analysis. LCTU will ensure that the study runs according to the pre-agreed timetable, ethical requirements are complied with, and that all aspects of the study are performed to the highest quality. LCTU will also be responsible for compliance with GCP and all regulatory requirements, including adverse event reporting, in conjunction with the Sponsor. The Senior Trial Manager will be responsible for the day-to-day management of the study.

14.2.7 Competing interests

None of the authors, co-applicants or those in supporting roles declare any competing interests.

14.2.8 Recognition of COVID-19 pandemic

Study recruitment will begin on commencement of the process evaluation (workstream 2), which is dependent on a number of dialysis units returning to their normal pre-COVID clinical service. In the event of further lockdown(s), patients would continue to attend the dialysis unit and so their participation in the study would not be impacted. As such, recruitment would continue and there would be no additional exposure as a result of research activities. The study team will work with participating sites to ensure that all research personnel follow local Trust COVID-19 guidelines ensuring the safety of staff and patients alike.

We are mindful of the impact of the post COVID-19 'new normal' context in hospitals and the possibility of future lockdown(s) on our plans for conducting the process evaluation (workstream 2, section 10.5), in particular undertaking observations in dialysis units and interviews with staff and patients. We will work closely with the PIs and unit managers at the sites sampled in order to establish which research activities are permitted and how these can be conducted, while complying with local Trust requirements. Given the observational work will take place over 42 months, it is likely that the COVID-19 situation and associated restrictions (in terms of research activities permitted), will vary; hence, we are planning for different eventualities. Depending on local Trust situation/restrictions, it may be possible to undertake observations as planned, as long as the researcher is complying with personal protective equipment (PPE) and distancing requirements of the Trust. For periods when restrictions do not allow observations on a unit, we will rely more heavily on interview data, and will explore ways of working with staff and patients to generate other forms of data (for example, more participatory approaches such as diary methodology and photovoice). Depending on the situation/restrictions, interviews with staff and patients may be conducted face-to-face (with appropriate PPE) or remotely (via telephone or approved video-conferencing software, e.g. Microsoft Teams, Zoom, Skype or Google Hangouts). We have also considered how the QuinteT Recruitment Intervention (workstream 3, section 10.6) processes can be conducted remotely if needed.

15. DISSEMINATION & PUBLICATION POLICY

The CI will be responsible for ensuring that the results of the study are disseminated through peer review journals, conference presentations and local mechanisms at all participating centres irrespective of the outcome within six months after the final study report. Authorship on the manuscript will be determined by the CI according to contribution to the study after discussion with the TSC, and according to the guidelines of leading medical journals. The TSC will be responsible for approval of all manuscripts arising from the study prior to submission for publication. All publications will quote the clinical trials registration number and will acknowledge the participating investigators, TSC and DSMC, LCTU, the Sponsor and the Funder. The study will be reported in line with the CONSORT statement, which is an evidence-based, minimum set of recommendations for reporting randomised trials.

The main output from the proposed study will be robust evidence of the clinical effectiveness and cost effectiveness of in-centre nocturnal haemodialysis. The results of this RCT will be disseminated with the following groups in mind:

15.1 Patient and Public Involvement

Previous PPI work has shown consensus that as many different methods as possible should be used to disseminate our results, due to the broad age range of our patient group. Annual newsletters will be sent to provide regular communication to participants. In addition, posters that will be displayed in waiting areas and receptions throughout the collaborating centres, patients and the public will be kept informed of the progress of the study through a study website constructed with input from our PPI team. The study team will also develop and lead dissemination through a Facebook page and Twitter feed. The PPI team will lead an open public dissemination event during, and at the end of the study. Our TMG is linked to the charity Kidney Research UK and will disseminate results of the study through the charity's website and newsletter. Through the University press office and utilising our relationship with Kidney Research UK, we will use press releases to alert the popular press and broadcasters to the study, publish articles in magazines such as the British Journal of Renal Medicine and the Journal of Kidney Care. The funding requested for PPI work includes attendance at UK Kidney Week for the purpose of disseminating results and experiences.

15.2 Nephrology community

A large multi-professional team including doctors, specialist nurses, renal technicians, pharmacists and dieticians typically manage patients with end-stage kidney failure in hospital and satellite dialysis centres. We will therefore target these groups through conferences, seminars and meetings. All key findings from the trial will be presented at national and international conferences such as the multidisciplinary UK Kidney Week (UKKW), which had over 1000 attendees in 2018; the European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) and the American Society of Nephrology Kidney Week. Support from international collaborators, including Professor Chris Chan (Toronto), Chair of the Frequent Haemodialysis Network, will also ensure international coverage upon study completion.

15.3 Wider clinical community and study impact

We will publish the protocol prior to the cessation of recruitment and at least one major peer-reviewed publication by the end of the study. We aim to publish the full results in a general medical journal such as the Lancet or New England Journal of Medicine, with the intention of reaching a global readership. The outputs will also include impact case studies to articulate the values emerging from the results of the study. The outcome of this research has the capacity to change UK and global practice. Through the expertise and standing of all the (co-)applicants, we anticipate that the findings of this study will be disseminated at local, national and international levels, as well as incorporated into national and international guidelines. Through the ongoing development of starter packs, there will already be a strategy to bridge the second translational (implementation) gap but we will continue to work through

patient networks clinical reference groups, and health care commissioners to ensure uptake and availability to patients as indicated by inclusion into new service specifications.

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17. APPENDICES

Appendix 1: Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
N/A – part of initial ethics submission	1.1	11 Dec 2020	Niamh Quann	• Section 10.11 – Compliance with study protocol. Correction of typographical error. If a participant allocated to the intervention arm receives less than 6 hours or more than 8 hours of HD delivered overnight, this **will** be reported as a deviation. Likewise, if a participant allocated to daytime dialysis receives less than 3 hours or more than 5 hours of HD delivered during the day, this **will** be reported as a deviation. • Section 14.2.8 – Recognition of COVID-19 pandemic. Duration of observational work changed from 24 months to 42 months as this was a typographical error.

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
Substantial amendment 01	2.0	24 June 2021	Niamh Quann Dr Matthew Graham-Brown Dr Katherine Hull Dr Victoria Cluley Dr Leila Rooshenas	• Page 1 - funding source and BHF logo added for CMR sub-study and CAG reference added for main study. • List of protocol contributors - Dr Matthew Graham-Brown, Dr Katherine Hull and Dr Victoria Cluley added. Job titles for Dr Helen Eborall and Dr Leila Rooshenas updated. • Section 1 - study summary. Montreal Cognitive Assessment (MoCA) added to the secondary outcome measures. • Section 4 - study design flow diagram. MoCA, cardiac MRI scan and pre and post dialysis blood tests added. • Section 8.3.2 – secondary outcome measures. MoCA and description added. • Section 8.3.2 – secondary outcome measures: measures of process. Wording updated to include Kt/V as an example measure of dialysis efficiency, in addition to urea reduction ratio. Iron prescription included in addition to ESA prescription. • Table 1: Schedule of assessments. MoCA, cardiac MRI scan and pre and post dialysis blood test added at relevant time points. • Section 10.5.2 – Process evaluation focus. Clarified that participants' interview data will be pseudo-anonymised rather than anonymised. • Section 10.5.3 – Process evaluation schedule.

				• Inclusion of a virtual, two-step, qualitative, exploration of usual care. Electronic consent added as an alternative to face-to-face consent. • Section 10.6.1 - Phase 1: Understanding recruitment (QRI). Text re COVID-19 considerations for the QRI moved from section 14.2.8 to section 10.6.1 to improve flow and clarity of text. • Clarification added that interviews will be conducted via telephone or a secure electronic platform where conducting these in person is not feasible. • New section (10.8 - NightLife-CMR: Cardiac MRI sub-study) and short paragraph added regarding the CMR sub-study. • Section 11.3 – reporting procedures for SAEs. Phosphataemia changed to hypophosphataemia. • Section 16 – References. References for the MoCA and photovoice method added. • Section 17 – Appendices. Appendix outlining a cardiac MRI sub-study added.

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

Substantial amendment 02	3.0	20/08/2021	Niamh Quann	• Abbreviations (page 9): Medical Dictionary for Regulatory Activities (MedDRA) added. • Section 1 – Study Summary (page 11): 'Adverse Events' changed to 'Serious Adverse Events' in secondary outcome measures. • Section 5 – Scientific Abstract. In relation to randomisation and stratification variables, 'site' changed to 'haemodialysis unit' to differentiate from Hospital Trust and to ensure consistency of wording within the protocol. • Section 8.3.2 – Secondary Outcome Measures (page 21-22): 'Adverse Events' changed to 'Serious Adverse Events'. • Section 10.2 – Table 1 – Schedule of Assessments (page 26). 'Review of consent' removed. • Section 11 – Adverse Event Reporting (page 43): Section title changed from 'Adverse Event Monitoring' to 'Serious Adverse Event Monitoring'. • Section 11.2 – Text updated to state data relating to Non-Serious Adverse Events will not be collected for this study. • Section 11.3 – reference to Adverse Events removed and text updated to differentiate between reporting SAEs on the SAE log and performing expedited reporting to the Sponsor. • Section 12.8 – Analyses of serious adverse events. Medical Dictionary for Regulatory Activities (MedDRA) will be used to tabulate and summarise SAEs by treatment group. • 'Adverse Event' changed to 'Serious Adverse Event' throughout the protocol.

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

Substantial amendment 03	4.0	20/03/2023	Niamh Quann Cassey Brookes Prof Laura Gray Dr Katherine Hull Ghazala Waheed Dr Shaun Barber Dr Matt Graham-Brown Hannah Worboys Dr Carmel Conefrey	• Page 1: EDGE ID updated due to merge of records. ISRCTN reference added for CMR substudy. NIHR logo updated due to name change in April 2022. • Page 5, Protocol Contributors: Cassey Brookes and Ghazala Waheed added. • Page 9, Abbreviations: NIHR updated due to name change in April 2022. • Page 11, Study Summary: – Randomisation ratio and recruitment sample size rearranged in the order of the groups stated immediately prior. – Secondary outcome #1 clarified to state total score (calculated from the KDQOL-SF) measured at 1, 3 and 6 months. – Secondary outcome added: KDQoL domains (calculated from KDQoL-SF) measured over 6-months with the following components: (a) physical component summary score; (b) mental component summary score; (c) kidney summary score; and (d) kidney disease component summary score. – Measures of safety clarified: SAEs in totality (rate/years), vascular access complications that lead to SAEs (rate/years); dialysis prescription changes that lead to SAEs (rate/years). – Measures of process clarified: hours per session, no. of sessions missed, no. of sessions not meeting time criteria, temporary change from treatment allocation. • Page 16, Scientific Abstract: updates to primary outcome measure and sample size information. • Page 20, Section 8, Study Design and Setting: – Section 8.1, Aims and objectives updated as per study summary. – Section 8.3.1, Primary outcome measure updated as per study summary. – Information added about 5-point difference and standardised difference. – Section 8.3.2, Secondary outcome measures updated as per study summary. – Text added to clarify measures of safety and measures of process as per study summary. – Participants and research teams will have the option to complete the questionnaires (except the MoCA) over the telephone to assist with data collection and to enhance convenience for the participant. • Page 27, Section 10.3, Randomisation: Clarification added regarding randomisation arms. Timeframe from randomisation to intervention added. • Page 27, Section 10.4.2, Stop-go criteria: Updates to the internal pilot progression criteria

				table to match accompanying text and acknowledge criteria around recruitment, participants and sites. • Page 33, section 10.5.4, Process evaluation analysis: Text added to clarify that anonymised copies of key documents for analysis will be stored on a secure University of Edinburgh drive by the workstream 2 lead. Addition of 'New Materialism' method of qualitative data analysis. • Page 38, section 10.3.6, QRI consent processes. Clarification about where and how consent can be obtained; in-person or remotely and in writing or verbally. More flexibility offered to reflect practice observed during the first year of recruitment. • Page 43, section 10.12, Compliance with study protocol. Definition of compliance added following DSMC recommendation. • Page 46, section 12.2, Power calculations: 5-point difference of the KDQoL between groups at 6 months changed to standardised difference of 0.26 in the KDQoL 36 total score between groups over 6 months, adjusting for baseline KDQoL 36 total score with correlation coefficient of 0.78. • Page 46, Sample size and justification: updated according to findings from the PIVOTAL trial. • Page 47, section 12.5, Analysis of primary outcome: Clarification added around intention-to-treat, linear regression and minimisation. • Page 48, Section 12.7, Analyses of secondary outcomes: Clarification added around the linear regression model. • Page 54, Section 14.2.5, Insurance and indemnity: Wording updated as per Sponsor request (UoL standard wording). – Page 59, References: Two references added for 'New Materialist' method of data analysis and the PIVOTAL trial. • Page 62, Appendix 2, NightLife-CMR: Text and flow chart updated to remove reference to specific site names as recruitment will be expanded to include other sites.

Appendix 2: NightLife-CMR: A cardiac MRI sub-study investigating the impact of in-centre nocturnal haemodialysis on cardiac structure and function

1. Background

Cardiovascular disease (CVD) is a significant health burden and leading cause of death for patients on haemodialysis. It is driven by clustering of traditional and non-traditional risk factors and has a limited response to traditional measures to reduce cardiovascular risk. Myocardial fibrosis is the common endpoint of these processes and accounts for much of the excess cardiovascular mortality. Conventional haemodialysis (i.e. 3.5-5 hours of in-centre haemodialysis, 3 times per week during the day) is a key component in driving the development of myocardial fibrosis due to recurrent episodes of myocardial ischaemia, rapid electrolyte changes and perpetuating systemic inflammation. In-centre nocturnal haemodialysis (INHD) is a way of providing extended-hours dialysis that potentially mitigates many of these non-traditional cardiovascular risk factors.

To determine the impact of INHD on cardiac structure and function, a separately funded sub-study (British Heart Foundation, ref PG/20/10132) will recruit 100 participants from the main NightLife study that has randomised participants to 6-months of INHD or conventional haemodialysis. Cardiac structure and function will be assessed by cardiac magnetic resonance imaging (CMR) and cardiac biomarkers levels pre- and post-intervention. Myocardial fibrosis will be characterised using native T1 mapping (cardiac MRI). Outcome data, including mortality, cardiovascular events and hospitalisation will be collected. This substudy will establish the effects of INHD on cardiovascular structure and function compared to CHD.

2. Rationale for including a CMR sub-study within the main NightLife study

The NightLife-CMR sub-study will assess whether extended hours, in-centre nocturnal haemodialysis is associated with a reduction in levels of myocardial fibrosis – a key determinant of patient outcomes. This multi-centre cardiac MRI sub-study will be delivered by a team with considerable experience across all areas of the study. The study is timely as it is patient-centred, with immediate possibilities to translation into clinical practice and addresses one of the core outcome measures identified as most important to patients on haemodialysis as well as stakeholders: cardiovascular health. This is the first randomised controlled trial to assess the effects of INHD on myocardial fibrosis and other prognostically important measures of CVD in this population, and we are uniquely placed in Leicester to be able to lead this study with expertise in delivery of clinical trials and the expertise in acquisition and analysis of the most pertinent CMR measures for this patient population.

3. Original hypothesis

6-months of INHD will result in a reduction in myocardial fibrosis assessed with native T1 mapping in comparison to CHD.

4. Study design

The design of this sub-study is the same as detailed in the main NightLife study protocol. It is a pragmatic, two-arm, multi-centre, randomised controlled trial assessing the effects of extended hours in-centre nocturnal haemodialysis on patient outcomes compared to standard care (daytime dialysis).

100 participants (50 from each randomised group) recruited to the main NightLife study will be eligible for inclusion in the CMR sub-study at participating sites with the capability of completing the additional CMR assessments and blood sampling. There will be no minimum number of participants required to be recruited from individual sites to the CMR sub-study, and target recruitment numbers at each site will be agreed individually with local teams.

At the centres where this sub-study is running, participants recruited to the NightLife study will have the chance to consent to undergo additional tests at the beginning and end of the study which will form the main outcomes from the sub-study. Participants recruited at centres where this sub-study is running can take part in the main NightLife study without taking part in sub-study.

5. Study population

The inclusion and exclusion criteria are the same for the NightLife study with the addition of contraindications to CMR scanning to the exclusion criteria.

5.1 Inclusion criteria

1. Patients established on haemodialysis for >3 months (i.e. prevalent dialysis patients)
2. Age ≥ 18 years
3. Ability to give written informed consent
4. Ability to participate fully in the interventions and follow-up procedures

5.2 Exclusion criteria

1. Currently on in-centre nocturnal dialysis, or less than 3 months since stopping
2. Less than 3 months since stopping extended daytime dialysis
3. Patients for whom extended dialysis is clinically indicated (e.g. calciphylaxis, pregnancy)
4. Scheduled for living donor kidney transplant
5. Plan to change dialysis modality or centre in the next 6-months
6. Life expectancy of <6-months
7. Current participation in an interventional trial with conflicting therapies or primary outcomes
8. Absolute contraindications to a cardiac MRI scan (CMR): non-conditional devices or implants; severe claustrophobia

6. Primary outcome measure

The primary outcome measure is the change in global myocardial native T1 time measured by CMR.

7. Secondary outcome measures

7.1 CMR

- Left ventricular mass, volumes and ejection fraction
- Peak systolic circumferential and longitudinal strain and early diastolic strain rates
- Aortic stiffness assessed with aortic distensibility and aortic pulse wave velocity • Native T2 mapping

7.2 Cardiac biomarkers

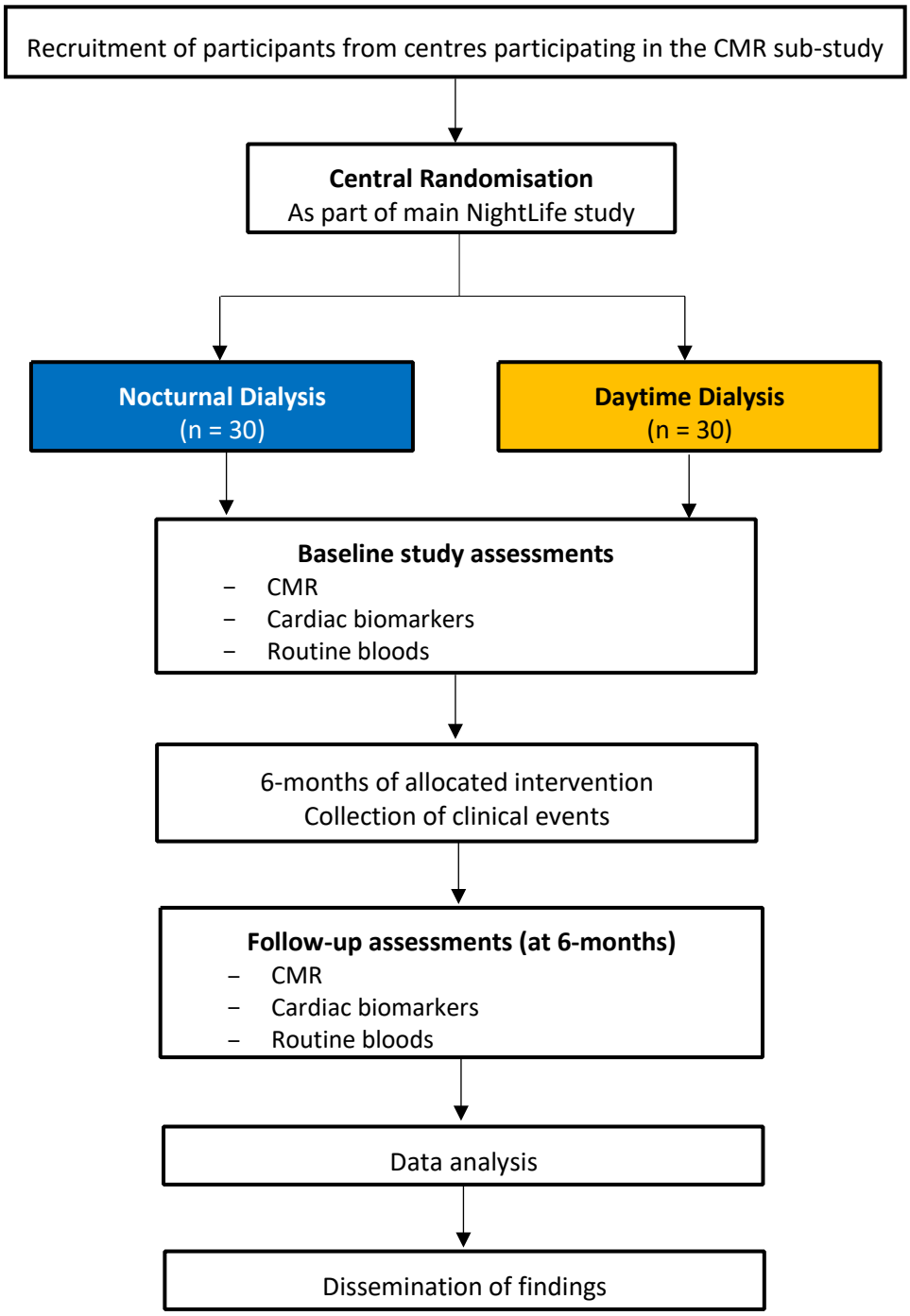
- Cardiac biomarkers will be collected pre and post dialysis at the start and end of the study, including:
- N-terminal fragment prohormone brain natriuretic peptide (NT-pro-BNP)
- High sensitivity cardiac troponin I (hs-cTnI)
- Soluble suppressor of tumorigenicity 2 (sST2)
- Galectin-3
- Fibroblast growth factor 23 (FGF23)
- Matrix metalloproteinase 1 (MMP-1)

8. Sub-study procedures

The target sample size for the NightLife-CMR sub-study is 100 (50 participants in each study arm). Recruitment will take place as demonstrated in Figure 5. The infrastructure for recruitment, randomisation and delivery for the intervention is already in place as part of the main NightLife study for all 3 centres participating in this sub-study. Additional consent will be sought for participants from the Nightlife study to join this sub-study.

Following recruitment and randomisation, participants will undergo baseline CMR and all other study investigations and undergo the same tests at 6-months. Participants will also have cardiovascular biomarker levels assessed pre and post dialysis at the start and the end of the study to assess the acute effects of the different dialysis regimens on circulating biomarkers of CVD and systemic inflammation. Clinical outcomes will be collected for all study participants for the duration of the study and for 5 years following study completion.

Figure 5: Flow diagram of CMR sub-study outline



8.1 Cardiac MRI scans

Participants recruited to the NightLife study at one of the centres participating in the NightLife-CMR substudy will be offered the opportunity to have a non-contrast cardiac MRI scan of their heart at baseline and 6-months to quantitatively define:

- Left and right ventricular structure and function
- Myocardial systolic and diastolic strain

- Myocardial tissue characterisation with native T1 and native T2 mapping • Aortic stiffness

A member of the study team will arrange a convenient time for participants to be scanned at the beginning and the end of the study on a non-dialysis day (not after the long inter-dialytic break) on a 3-Tesla platform at each site participating in this sub-study. Scan data will be anonymised at the point of scanning and transferred to Leicester for analysis through the secure NHS scan transfer system (free from any associated patient identifiable information) or on an encrypted NHS hard-drive.

8.2 Blood biomarkers

Blood samples will be collected from the arterial needle by dialysis nursing staff. Once collected, the samples will be centrifuged and the serum will be stored at each participating centre. At the end of the study samples will be transferred to Leicester for batch analysis.

Participants who agree to take part in the CMR sub-study will also have an additional 30ml of blood taken at the start and at the end of dialysis at baseline and 6-months to assess changes in measures of blood biomarkers of cardiovascular disease. These blood tests are not part of routine care, however will be collected at the same time as the insertion and removal of the participant's dialysis needles to ensure no further venepuncture is required.

Blood will be spun and stored locally at each of the participating sites and stored in -80°C freezers and transferred via courier for central analysis at the University of Leicester in batches throughout the study. No participant identifiable information will be transferred with blood samples during transit.

9. Power calculation

Data from the pilot study (the MIDNIGHT study) informs the power calculation for this study. The MIDNIGHT study demonstrated that 6 months of INHD resulted in a 30ms reduction in global native T1 time compared to controls, with a change in standard deviation of native T1 from pre and post intervention of 47ms. Based on this data, to detect a between group difference in native T1 time of 30ms with 80% power (α=0.05) requires 40 participants in each study arm (80 participants in total). To account for a 25% dropout rate, oursample size is 50 participants in the intervention group and 50 participants in the control group (100 in total).

10. Data management

LCTU will be the co-ordinating centre for the main NightLife study with additional support from the NightLife-CMR research team to deliver procedures related to the CMR sub-study. Whilst all data relating to the main NightLife study will be held by LCTU, data from the CMR analysis and blood biomarker analysis will be held separately, securely and anonymously free from any patient identifiable information on secure NHS servers at the University Hospitals of Leicester that only members of the study team will have access to. This will be linked to relevant participant demographic information at the end of the study when the database for the study is locked.

10.1 Cardiac MRI data

Cardiac MRI scans will be anonymised at the point of scan at each of the participating centres so that they are free of any patient personal identifying information. These scans will be stored locally on NHS servers and transferred through a secure electronic NHS scan transfer portal from each of the participating centres

to Leicester for analysis. In the event that the scan transfer portal is not available the scan will be transferred on encrypted NHS hard-drives between centres free of any patient identifiable information. All analysis will be conducted by an assessor blinded to any patient data or intervention allocation.

11. Assessment and management of risk

There are minimal risks associated with taking part in the sub-study and participants will be made fully aware of any risks before consenting. All research investigations are detailed in the participant information sheet and will also be explained to the participant before each investigation to ensure that they are willing to undertake each one. In addition to the risks outlined in the main NightLife study protocol, the following potential risks and burdens relate specifically to the NightLife CMR sub-study.

Cardiac MRI scans will be undertaken according to standard operating procedures at each of the participating sites. All cardiac MRI scans will be supervised by a qualified research radiographer. All participants will be screened for the presence of contraindications to MRI as per standard MRI safety policies:

- Permanent pacemaker or ICD
- Brain Aneurysm Clip
- Implanted neural stimulator
- Cochlear implant (specific implant must be checked that it is MR safe)
- Ocular foreign body (e.g. metal shavings) Unless removed
- Other implanted medical devices: (e.g. Swan Ganz catheter)
- Insulin pump
- Metal shrapnel or bullet

The scan will take around 40 minutes during which time the patient will be lying within the MRI scanner. They will be asked to breathe in and out and hold their breath for short periods. Some participants can find this claustrophobic, however they will be in constant communication with research staff and the session can be terminated at any time and the participant can be removed from the scanner. The MRI scan is a non-contrast and non-stress scan, so there are no additional risks from any pharmacological agents and patients do not have to stop any medications prior to the scan.

12. Patient and Public Involvement (PPI)

Patients and the public have been involved in the concept, scope and design of this CMR sub-study from the very outset, and will be actively involved during the duration of the study. The need for this sub-study was borne out of discussions with local PPI groups and to align with the Standardised Outcomes in Nephrology (SONG-HD) initiative core outcome measure for trials of patients on haemodialysis. In addition to the extensive patient and public involvement and engagement (PPIE) planned to run alongside the main NightLife study, PPI groups are planned for the beginning of the CMR sub-study, partway through recruitment to discuss progression and on study completion to assist dissemination plans.