Prepare for Kidney Care: a randomised controlled trial of preparing for responsive management versus preparing for renal dialysis in advanced kidney disease

THE PREPARE FOR KIDNEY CARE TRIAL

PROTOCOL

Approvals and IDs	*Reference*
Protocol version	Version 9.0, 20 Nov 2023
IRAS project ID	215616
REC Reference	17/SC/0070
North Bristol NHS Trust (R&I)	3858
ISRCTN	17133653
Funder (NIHR HTA)	15/57/39
NIHR CRN Portfolio	32254

This protocol has regard for the HRA guidance and order of content

Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
Pre-approval	1.1	26.01.2017	FJC	NBT and UoB logos added; sponsor email and telephone contact details updated;
Pre-approval	1.2	6.02.2017	FJC	Added friend to "family member/ friend/ carer"; Added section on finding a personal (or nominated) consultee if participation loses capacity.
Pre-approval	2.0	30.03.2017	FJC	Changed long and short study name. Inserted Trial Manager details. Changed the name of one treatment arm from 'conservative care' to 'responsive management'. Amended trial flow chart to reflect above changes and to give a more balanced overview of treatment arms. Additional information about what happens if there is loss of capacity in patients who have already consented to participate in the RCT.
Pre-approval	3.0	05.05.2017	FJC	Clarification in introduction/ background that the observational studies have also looked at preparation for dialysis and conservative care. Change to arrangements so that patients that lose capacity are withdrawn from the study.
Post-approval	3.1	27.06.2017	FJC	Removing minimisation by rate of eGFR decline from randomisation process. Correcting some references to old terminology (assess and launch/ maintain/ support enhancement).
Post-approval	4.0	09.09.2017	FJC	Allowing 1-3 home visits as part of Assess phase of prepare for responsive management, as indicated clinically. Clarifying the operational definition of

				CKD5 in the eligibility criteria section. Allowing shared care with primary care in the prepare for responsive management arm. Defining frequencies and windows for research and clinical visits.
Post-approval	5.0	12th November 2018	FJC	Changes to responsive management intervention: introducing the concept of routine support (with one home visit per year instead of alternating clinic/ home visits) and responsive support in renal outpatients and in the community. Change to the eGFR eligibility criterion to a single eGFR <15 mL/min/1.73m^2 that is not considered to be due to acute kidney injury by the clinical team.
Post-approval	6.0	17th March 2020	FJC	Responding to the clinical and logistic challenges of COVID-19: changes to allow telephone reviews to replace some face-to-face research and clinical activity.
Post-approval	7.0	2nd August 2020	FJC	Responding to the clinical and logistic challenges of COVID-19: changes to allow greater flexibility to conduct clinic and home-visits by telephone/ video communication as deemed appropriate. Updating non-compliance and clarifying withdrawal criteria. Updating the end date for the trial following an agreed extension to recruitment by the funder.
Post-approval	8.0	26 April 2021	FJC	Update of safety reporting section to clarify that only related and unexpected SAEs require expedited reporting, whilst all other SAE data is collected on the study CRFs. Clarification of duration of patient participation in the study. Clarification of routine data collection in the event of a patient losing capacity. Correction of references and removal of superfluous information. Update of trial manger details.
Post-approval	9.0	20 November 2023	FJC	Updated contact details for study team. Study end date updated. Updated name of CTU. Clarification on the eligibility criteria of eGFR<15 in the 12 months proceeding consent. Inclusion of Sealed Envelope as new randomisation system. Clarification of blinding procedures and interim analyses, required modality of RCT follow up contacts, staff able to consent patients into the study, symptom checklist

				requirements, access to the final trial dataset, and role of the PAG. Updated archiving period.

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

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 clinical 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.

For and on behalf of the Study Sponsor:

Signature:
.....

Date:
...../...../.....

Name (please print):
.....

Position:
.....

Chief Investigator:

Signature:
.....

Date:
...../...../.....

Name: (please print):
.....

KEY TRIAL CONTACTS

Chief Investigator	Professor Fergus Caskey University of Bristol Population Health Sciences, Bristol Medical School Canynge Hall, 39 Whatley Road Bristol BS8 2PS Telephone: 0117 928 7290 Email: fergus.caskey@bristol.ac.uk
Trial Manager/Coordinators	Alex Soundy/Jo Worthington/Jessica Frost University of Bristol Population Health Sciences, Bristol Medical School Canynge Hall, 39 Whatley Road Bristol BS8 2PS Telephone: 0117 455 9046 Email: prepare4kc@bristol.ac.uk
Lead Research Nurse	Ms. Karen Alloway Clinical Research Centre Southmead Hospital Westbury-on-Trym Bristol BS10 5NB Telephone: 0117 414 8108 Fax: 0117 41 49329 Email: karen.alloway@nbt.nhs.uk
Co-investigators	Professor J Athene Lane, Professor in Clinical Trials, University of Bristol Professor Jenny Donovan, Professor of Social Medicine, University of Bristol Mrs Denise Abbott, Patient and Public Involvement, North Bristol NHS Trust Dr Leila Rooshenas, Lecturer in Qualitative Health Science, University of Bristol

	Professor Fliss Murtagh, Professor in Palliative Care, Hull York Medical School Professor Christopher Salisbury, Professor in Primary Health Care, University of Bristol Dr Emma Murphy, Advanced Nurse Practitioner/Clinical Lecturer in Palliative and End of life Care, University of Southampton Dr Joseph Chilcot King's College London Professor Paul Roderick, Professor of Public Health, University of Southampton Professor Yoav Ben-Shlomo, Professor of Clinical Epidemiology, University of Bristol Professor Ken Farrington, Consultant Nephrologist, East & North Hertfordshire NHS Trust Dr Hugh Rayner, Consultant Nephrologist, Heart of England NHS Foundation Trust Professor Aine Burns, Consultant Nephrologist, Royal Free Hampstead NHS Trust Professor Simon Davies, Consultant Nephrologist, University Hospitals of North Midlands NHS Trust Professor Joanna Coast, Professor in the Economics of Health and Care, University of Bristol Professor Richard Huxtable, Professor of Medical Ethics and Law, University of Bristol Dr Stephanie MacNeill, Research Fellow in Medical Statistics Dr Andrew Gibson, Associate Professor in Patient and Public Involvement, University of the West of England
Lead Statistician	Dr Stephanie MacNeill, Research Fellow in Medical Statistics Please use BTC postal address Telephone: 0117 455 2564 Email: stephanie.macneill@bristol.ac.uk

TRIAL SUMMARY

Trial Title	Prepare for Kidney Care: a randomised controlled trial of preparing for kidney dialysis versus preparing for responsive management in advanced kidney disease
Internal ref. no. (or short title)	Prepare for Kidney Care
Trial Design	A randomised controlled trial comparing two care pathways
Trial Participants	Multi-morbid, frail, older patients with advanced chronic kidney disease
Planned Sample Size	512
Treatment duration	End of data collection
Follow up duration	End of data collection
Planned Trial Period	01/01/2017 – 31/08/2025
Aims	To establish the effectiveness and cost-effectiveness of preparing for responsive management compared with preparing for dialysis in relation to quality and length of life in multi-morbid, frail, older people with failing kidneys.

FUNDING AND SUPPORT IN KIND

Funder(s) (Names and contact details of ALL organisations providing funding and/or support in kind for this trial)	**Financial and non-financial support given**
NIHR Health Technology Assessment Programme National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre University of Southampton Alpha House Enterprise Road Southampton SO16 7NS Telephone: 023 8059 5586 Fax: 023 8059 5639 Email: htaoas@southampton.ac.uk	Grant funding
Bristol Trials Centre (BTC) Population Health Sciences, Bristol Medical School University of Bristol 1-5 Whiteladies Road Bristol BS8 1NU Telephone: 0117 455 1230 Email: btc-mailbox@bristol.ac.uk	Methodological expertise
Research & Innovation North Bristol NHS Trust Floor 3 Learning & Research building Southmead Hospital Westbury-on-Trym Bristol, BS10 5NB Telephone: 0117 414 9330 Fax: 0117 414 9329 Email: researchsponsor@nbt.nhs.uk	Sponsorship
UK Renal Registry	Partner

Floor 3 Learning & Research building Southmead Hospital Westbury-on-Trym Bristol, BS10 5NB Telephone: 0117 414 8150 Email: renalregistry@renalregistry.nhs.uk	

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Overall Project management

The Chief Investigator will take overall responsibility for managing the various components of the trial and will meet at least monthly with the leads for each component. Years 1-2 the CI will be establishing the trial, supported by the lead renal research nurse. From a technical and strategic perspective, the CI will be advised and supported by the QuinteT team (responsible for delivering the 'QuinteT Recruitment Intervention', QRI) and the Bristol Trials Centre (BTC).

The Clinical Trial*:* The BTC is a UK Clinical Research Collaboration (UKCRC) registered trials unit, and they will manage the trial on a day-to-day basis.

Patient Advisory Group

A Patient Advisory Group will meet 6 monthly in years 1-2, then annually. This will be co-chaired by the two PPI co-applicants.

Trial Management Group

A Trial Management Group (TMG) will meet at least once each month in the first 6 months, then 6 monthly to review progress, with potential for additional ad hoc meetings, as required/indicated. This will be chaired by Dr Fergus Caskey (CI) and will consist of representatives from the study office including the sponsor and relevant co-applicants. Meetings will be in person and by teleconference to maximise attendance.

Independence

For the TSC and DMC, independence is defined by the NIHR HTA 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.*

Trial Steering Committee

The role of the Trial Steering Committee (TSC) is to monitor and supervise the progress of the trial on behalf of the Sponsor and Funder and to ensure that the project is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice. The TSC will be chaired by an independent member and comprise five additional independent members (covering expertise in trial statistics, nephrology, palliative care, health economics and PPI). The trial manager and the CI (Dr Fergus Caskey) will also be formal members of the TSC, maintaining its membership independence at 75%. Observers may also attend, as may other members of the TMG or members of other professional bodies, at the invitation of the Chair. The TSC will meet for the first time by month 6 of the trial and then at least every 6 months.

Data Monitoring (and Ethics) Committee

An independent Data Monitoring Committee (DMC) will meet with the purpose of reviewing the accumulating data at pre-specified intervals to advise the TSC and the sponsor regarding patient safety and the ethical running of the trial. They will make recommendations to the TSC as to whether there are any ethical or safety issues that may necessitate a modification to the protocol or closure of the trial. Prof Colin Baigent, a clinical epidemiologist and highly experienced Clinical Trialist from Oxford Clinical Trial Service Unit, will be the independent chair for this committee. The DMC will comprise two additional independent members (covering expertise in trial statistics, nephrology and palliative care). The DMC will meet for the first time by month 6 of the trial and then at least every 12 months, but more frequently if indicated.

Contents

Tables

LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BTC	Bristol Trials Centre
CA	Competent Authority
CI	Chief Investigator
CKD	Chronic Kidney Disease
CRF	Case Report Form
CTAR	Clinical Team Activity Record
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
eGFR	Glomerular Filtration Rate
EQ-5D-5L	The EuroQOL 5-dimension, 5-level
ESKD	End Stage Kidney Disease
GCP	Good Clinical Practice
GP	General Practitioner
ICECAP-O	The ICEpop capability measure for older people
ICECAP-SCM	The ICEpop capability measure for supportive care management
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
iPOS-S renal renal	The integrated palliative outcome scale – symptoms
ISF	Investigator Site File
ISRCTN Number	International Standard Randomised Controlled Trials
MDT	Multi-Disciplinary Teams
MTBQ	Multimorbidity Treatment Burden Questionnaire
NHS	National Health Service
NHS R&D	National Health Service Research & Development
NICE	National Institute for Health and Care Excellence

NIHR	National Institute for Health Research
PAG	Patient Advisory Group
PD	Peritoneal Dialysis
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QA	Quality Assurance
QALY	Quality Adjusted Life Year
QC	Quality Control
QoL	Quality of Life
QP	Qualified Person
QRI	QuinteT Recruitment Intervention
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSI	Site Specific Information
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
UK	United Kingdom
UKRR	United Kingdom Renal Registry
UoB	University of Bristol
WHO	World Health Organisation

TRIAL FLOW CHART

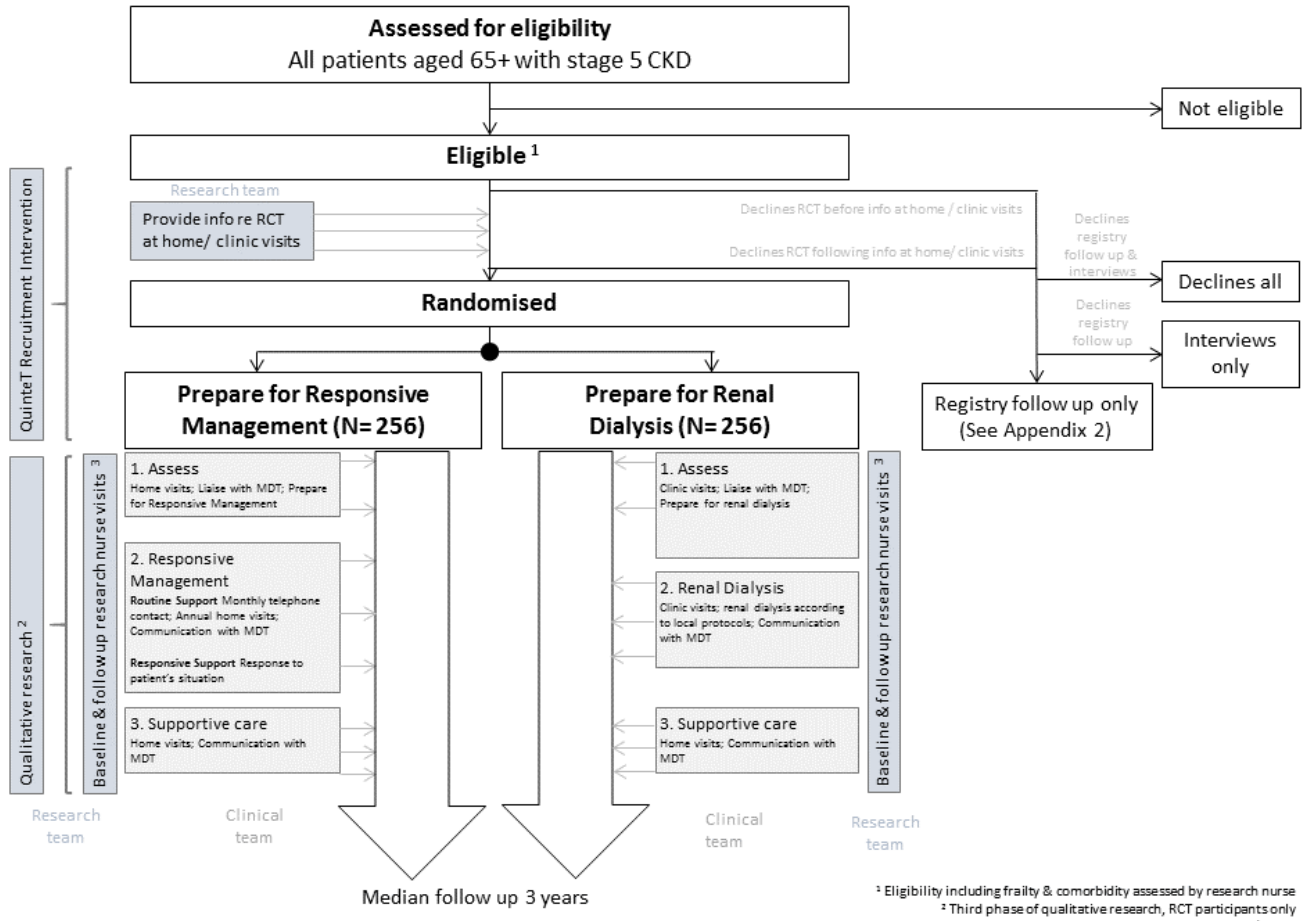

Figure 1. Flow of potential participants in Prepare for Kidney Care

- All face-to-face contact will follow strict social distancing protocols, in line with local Trust policies. If there is an over-riding infection control reason why any of the face-to-face visits above (clinic or home visits) cannot take place, then they can be undertaken remotely by telephone/ video communication, as deemed appropriate.

1 BACKGROUND

Every year in the UK more than 3,500 people aged 65+ develop symptomatic kidney failure – ESKD – and start dialysis [1]. This number continues to rise in the elderly [1, 2]. Transplantation is not an option for most of these patients, and while dialysis extends life for some, the associated survival and health-related quality of life benefits are uncertain. Conservative care packages exist (comprising all aspects of care without preparing for dialysis), but their content and availability varies widely [3]. Dialysis has a considerable impact on daily life. Of patients aged 65+ commencing dialysis, 86% receive haemodialysis (three times a week for four hours up at a hospital) and 14% receive peritoneal dialysis (four times a day for 30 minutes, or overnight by machine, at home) [1]. Preparation for this must start months in advance, as patients have to choose a treatment option and undergo any necessary surgery for dialysis access. As they develop symptoms and start dialysis at different levels of kidney function, knowing when to begin preparation is difficult. Although their prognosis is well documented (55% of 65-74 year olds and 40% of 75+ year olds survive 3 years [4]), it is not known how long they would have lived without dialysis. Further, the commencement of dialysis can be associated with a sharp drop in functional status [5].

Some patients aged 65+ choose not to prepare for dialysis and instead prepare for conservative care. Evidence of the comparative effectiveness of these approaches is entirely observational and so prone to bias, confounding by indication and difficulty in knowing when to begin the comparison in the comparator, non-dialysis arm. What evidence there is suggests equivalent survival in several patient groups – those aged 70+ with a WHO performance status of 3+ [6], those aged 75+ with two or more comorbidities [7] and those aged 80+ regardless of comorbidity [6]. QoL has been reported in 5 studies [8-12]. At baseline, SF36 physical component scores were significantly lower in patients choosing conservative care compared with dialysis, whilst the mental component scores were similar [8-10]. During follow up, the trajectory of QoL tends to remain similar until initiation of dialysis with improvement in some domains but significant declines in others – Satisfaction with Life Scale [9], and the KDQol parameters effect of kidney disease and burden of kidney disease [12]. QoL is also significantly affected in carers of dialysis patients [13] and the experience of caring for conservative care patients presents substantial difficulties [14].

The uncertainty about the relative benefits of preparing for dialysis and preparing for conservative care is reflected in the variations in practice. A 2013 survey of UK renal units showed great variability in the proportion of patients “choosing” conservative care depending on where they were being looked after [3].

A systematic review of the literature covering up to 2012 [15] identified three observational cohort studies of suitable quality [7, 16, 17]. Considering the heterogeneity of study design, potential confounders and high risk of bias, the authors concluded that it was difficult to make any recommendations for clinical practice. They did, however, remark that any survival advantage of preparing for dialysis in patients aged 65+ appeared to be lost in the presence of severe co-morbidities or very poor functional performance [15]. They highlighted the need for more evidence,

particularly in those aged 75+, and emphasised the importance of collecting data on QoL and symptoms [15].

National and international research charities have indicated the importance of this topic by funding exploratory and observational (but not RCT) studies: The NIHR CKMAPPs Study undertook interviews with staff and patients and a survey to establish attitudes towards conservative care and practices in UK renal units [3, 18-20]; The European EQUAL Study [21], French CKD-REIN Study [22] and Dutch PREPARE-2 Study [23] are all observational multi-centre cohort studies of pre-dialysis patients which rely on statistics to adjust for inherent bias and confounding. None are powered to compare preparation for dialysis and preparation for conservative care. In the UK there is also the observational matched cohort study of dialysis versus conservative care UK Frail and Elderly Patient Outcomes on Dialysis (FEPOD) Study part II.

2 RATIONALE

With the UK population aged 65+ predicted to increase by 60% (from 10.3m to 16.9m) by 2035 [24] and health care costs increasing [25], the optimal management of frail, multi-morbid people with advanced chronic kidney disease will remain highly relevant to the NHS. The importance of end of life kidney care was recognised in 2005 in Part 2 of the National Service Framework [26]. More recently it has been targeted by the KDIGO initiative which held a consensus meeting to coordinate efforts in this area [27]. Given the human and economic impact of dialysis in older people, there is a pressing need to establish the comparative effectiveness and cost-effectiveness of a prepare for conservative care pathway against the existing 'prepare for dialysis' pathway. First and foremost, this study will provide high quality robust evidence to inform multi-morbid, frail, older patients, their relatives and their clinical teams when making extremely difficult decisions about whether to prepare for dialysis or prepare for conservative care. The current variation in rates of patients aged 75+ choosing not to have dialysis [3] cannot be due to patient factors and likely reflects, at least in part, differing interpretation of the observational data by health professionals talking to patients when they are deciding which treatment to choose. This variation should be reduced. The timing also allows us to capitalise on the UK Renal Registry's novel permissions to capture routine health data on all patients in secondary care with an eGFR less than 30 ml/min/1.73m^2, which covers all patients eligible for Prepare for Kidney Care. The Prepare for Kidney Care trial is effectively embedded in the UK Renal Registry which has 100% coverage of the UK. This will allow the generalisability of the trial findings to be ascertained.

If dialysis is started it is expensive. Haemodialysis costs £25k per patient per year and peritoneal dialysis £20k per patient per year – around £500m of NHS spending each year [28]. A further £75m is spent on hospital admissions and £50m on transport to and from dialysis [28]. The cost of conservative care is hard to estimate as there is wide variation in what is delivered [18, 27]. In the UK, only half of renal units offer advance care planning and less than half offer psychological support, occupational health or social worker review, or home visits by renal staff [3]. It is known, however, that patients who choose conservative care are more likely to die at home or in a hospice, as many would wish, and are less likely to be admitted to hospital [29].

The importance of end of life kidney care was recognised in 2005 in Part 2 of the National Service Framework [26]. More recently it has been targeted by the KDIGO initiative which held a consensus meeting to coordinate efforts in this area [27].

A systematic review of the literature looking for studies comparing dialysis and conservative care up to 2012 [30] identified three observational cohort studies of suitable quality [7, 15, 29]. There is even less data comparing the associated quality of life. It is not known how patients value prolongation of life over quality of life when faced with such a life changing decision.

Uncertainty in this area is demonstrated by the wide variation in reported rates of conservative care in patients aged 75+ in renal units around the UK (from 5-95%) and variation in the components of the conservative care pathway in these renal units, as demonstrated in the NIHR HS&DR funded CKMAPP Study [3].

The morbidity and medicalisation of life associated with preparing for dialysis makes the decision very difficult for patients with kidney failure and their families. They need good information to inform their decision making, and this is critically important given the considerable burden of dialysis treatment; if benefit of preparing for dialysis over preparing for conservative care is limited, we need to quantify and characterise this, so as to better inform dialysis decision-making.

The difference between the two pathways is that patients randomised to prepare for responsive management (an optimised form of conservative/ supportive care that has been developed with experts and patients specifically for this study) will have regular support from the renal unit staff (assessment of their symptoms and priorities for care at home visits and by telephone/ video communication) and support that responds to their needs (from renal unit staff, palliative care teams and community staff). They will avoid the scans and surgery that normally take place when patients prepare for dialysis and therefore any complications of that access surgery. The aim of the pathway is to support patients and respond to their needs in their preferred place of care so that they do not feel they have to swap to dialysis to feel safe and be kept comfortable if/ when they develop ESKD. This pathway is based on international guidance [27] and UK expert consensus with PPI involvement.

The results from Prepare for Kidney Care will therefore be immediately useful to patients facing kidney failure, healthcare professionals and policy makers.

First and foremost this study will provide high quality robust evidence to inform older patients with comorbidities their families/carers and clinicians when making extremely difficult decisions about whether to prepare for dialysis or conservative care.

Also novel is use of the UK Renal Registry's (UKRR) new permissions to capture data on all patients meeting the Prepare for Kidney Care age and kidney function eligibility criteria in secondary care, allowing the generalisability of the trial findings to be ascertained. Qualitative methods will be used to optimise the design of the RCT during the development phase. Throughout recruitment, integrated qualitative methods will be used to identify barriers and optimise information provision and trial participation [31]. Qualitative research will also investigate how components of the two treatment pathways have worked for patients and their families and help interpret results.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

The aim of the trial is to establish the effectiveness and cost-effectiveness of preparing for responsive management compared with preparing for dialysis in relation to quality and length of life in multi-morbid, frail, older people with advanced CKD.

3.1 Primary objective

To determine the relative effectiveness of preparing for responsive management versus preparing for dialysis on quality adjusted life years (QALYs) after three years in an individual-level pragmatic RCT in multi-morbid, frail, older patients with advanced CKD.

3.2 Secondary objectives

1. To determine the effect of the intervention on:
   i) Survival
   ii) Hospital-free days
   iii) Patient reported outcomes: generic & disease specific QoL (EQ-5D-5L & POS-S renal), capability gain (ICECAP-O & ICECAP-SCM), patient treatment burden (MTBQ) & impact on carers
   iv) Cost-effectiveness: Incremental cost-per QALY gained, and equivalent years of full/sufficient capability gained.
2. To fully understand the external validity of the trial through screening logs and linkage to the UK Renal Registry's new database of all patients in secondary care with CKD stages 4 and 5.
3. To explore patients', relatives', and health care professionals' perspectives on the acceptability of preparation for dialysis and preparation for responsive management.

3.3 Outcome measures

3.3.1 Primary outcome

The primary outcome is the mean total number of QALYs observed in the two arms between 2 August 2017 (first patient recruited) and the end of data collection, using the EQ-5D-5L measured 4 monthly during this period to derive the health utility value and appropriate imputation methods for missing values. After death, patients are allocated a utility value of 0 therefore continue to contribute data to the study until the end of data collection, regardless of survival. Based on projected recruitment patterns, we estimate we will have, on average, 3 years of utility value data on patients on which to calculate QALYs.

This outcome has been chosen after extensive discussion with patients and patient groups who are very clear that they care about quality of life and quantity of life and evidence that patients may be willing to forgo some quantity of life for better quality of life [32].

3.3.2 Secondary outcomes

Survival related

- All-cause mortality
- Cause-specific mortality
- Place of death
- Hospital-free days alive

Patient reported outcome related

- Generic quality of life (EQ-5D-5L [33])
- Disease specific quality of life/symptom burden (POS-S renal [34])
- Capability gain specific to older persons (ICECAP-O [35])
- Capability during end-of-life care (ICECAP-SCM [36])
- Patient treatment burden (MTBQ) [37]

Physical functioning

- Timed get up and go [38] – summary score at 12 monthly time points and changes over time
- Grip strength (Jamar hand dynamometer) [39] – summary score at 12 monthly time points and changes over time

Relative/carer reported outcomes

- Impact on carers [40]
- QUALYCARE post-bereavement survey obtaining retrospective information covering the 1 week preceding death if the patient dies [41].

Health economic

- Incremental cost-per QALY gained from the health perspective
- Cost per equivalent year of full/sufficient capability gained, from health and societal perspectives.

4 TRIAL DESIGN

This study is a two-arm, superiority, parallel group, non-blinded, individual-level, pragmatic RCT in multi-morbid, frail, older people with advanced CKD, comparing the QALYs gained over three years after preparing for responsive management versus preparing for dialysis.

Qualitative and mixed methods are integrated throughout the trial to optimise its design and delivery. These will proceed in three interconnected stages: optimising the trial intervention (stage 1), optimising recruitment (stage 2), and understanding the acceptability of the intervention and reasons for non-compliance (stage 3).

5 STUDY SETTING

This is a national, multi-centre trial recruiting patients from secondary care renal units, but with the intervention – preparation for responsive management– delivered predominantly in the community.

To participate, renal units must provide a pre-dialysis service and be willing to allow some patients to enter the trial. Eligible patients will already be attending the pre-dialysis service, either in a general CKD clinic or a specialised low-clearance/pre-dialysis clinic. Sites must also be able and willing to provide the intervention arm of the treatment, which includes having:

- Healthcare professionals able and willing to provide clinical assessments and care coordination in the patient's home, where this is appropriate considering patient and staff safety, and
- Local palliative care/hospice services that are willing to support patients if they progress to the "supportive care" phase.

Not all healthcare professionals in a site need to agree to participate in the trial. The list of currently participating sites can be found on the trial website (http://www.bristol.ac.uk/prepare-kc-trial/).

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

Patients known to renal services with new or existing stage 5 CKD[1] and

- Aged 65+ with a World Health Organisation (WHO) performance status 3+ [6] [2], or
- Aged 65+ with a Davies co-morbidity score 2+ [42][3], or
- Aged 80+ [6].

6.2 Exclusion criteria

- Unable to consent, e.g. significant cognitive impairment or psychiatric disorder
- Not medically fit for dialysis
- Within 4 weeks of needing to start dialysis.
- Have had a previous kidney transplant
- Are 'active' on the kidney transplant waiting list or being worked up for the kidney transplant waiting list

6.3 Inclusion criteria for family members, friends and carers

With the patient's consent, family members, friends and carers will also be recruited to the qualitative work packages if they are:

- Aged 18+ and
- Identified by the patient as the person closest to them, usually a family member, close friend, informal caregiver or neighbour and
- Able to give informed consent and to complete the questionnaires

[1] Defined as an eGFR <15 within the 12 months preceeding consent that is not considered to be due to acute kidney injury by the clinical team. The patient is still eligible if there are some results just above this range during screening or follow up.

[2] 0 = Fully active, able to carry out all normal activity without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 2 = Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours; 3 = Symptomatic and in a chair or in bed for greater than 50% of the day but not bedridden; 4 = Completely disabled; cannot carry out any self-care; totally confined to bed or chair. As assessed during the screening period.

[3] Each of the following scores one point: Malignancy, ischaemic heart disease, peripheral vascular disease (including stroke), left ventricular dysfunction, diabetes mellitus, systemic collagen vascular disease, other significant pathology (including COPD, cirrhosis, psychiatric illness, HIV).

7 TRIAL PROCEDURES

A schedule of procedures is included as Appendix 17.1.

7.1 Recruitment

7.1.1 Patient identification and screening for eligibility

In sites taking part, the normal clinical teams looking after patients approaching ESKD will be made aware of the trial including the information that will be being disseminated to potential participants. It is extremely likely that patients will want reassurance from their normal clinical teams that the trial is appropriate for them.

A range of approaches will be used by clinical teams to identify patients, depending on their computer system and how they organise their clinics. If they run specialised "low clearance" or "pre-dialysis" clinics for patients approaching ESKD then clinic lists will be searched to identify potential participants. Electronic and paper records will be checked for eligibility. Alternatively, if patients approaching ESKD are seen in more general kidney clinics then electronic and paper records will need to be searched more widely to identify potentially eligible participants who can then be vetted for eligibility.

Eligibility will be assessed by nurses with the assistance of doctors where required. All eligible patients will be documented in a comprehensive screening log, which will be developed in collaboration with the QuinteT team (see Section 9.3). If the normal clinical team decides for any reason that an eligible patient should not be offered information about the trial, then this will be documented on the screening log with the reasons.

A standard Patient Invitation Letter will be handed to eligible patients in clinic by their normal care team or sent out to eligible patients introducing the study, as deemed most appropriate by the normal care team. This will be accompanied by the appropriate patient information sheets (introductory, qualitative, RCT and/ or RFU). Information sheets will inform people that research-related telephone/ video communication and meetings may be recorded with permission to inform staff feedback/training to improve the clarity of information provision about the trial.

Given the complexity of what is being discussed and the importance of involving relatives and others whose opinions they trust, these discussions will take place at up to three home, specialist clinic visits, research clinic visits or telephone/ video communication contacts. While we anticipate that these visits would be optimally performed at the patient's home (adhering to local infection control and social distancing policies), they do not have to be; they should be arranged where it is most convenient for the patient and their family and somewhere conducive to them taking on board all the information about the trial. These arrangements will be individualised according to local circumstances in each site with some/ all discussions being done remotely by telephone/ video communication methods, where appropriate.

During the information-giving discussions, the research team will explore the patient's current health state and any ESKD treatment decisions that have already been made. They will explain the

trial and what taking part entails and, with the patient and family members/ friends/ carers' consent these discussions will be recorded to allow recruitment issues to be identified (see Section 9.3).

When the patient and their family/ friends/ carers feel fully informed, they will be asked to make a decision about entering the RCT.

If they decide to enter the trial, the research team will:

- Obtain consent for the RCT
- Conduct the baseline interview, physical assessment and administer the questionnaires
- Allocate the patient to their treatment arm, i.e. prepare for responsive management or prepare for dialysis
- Explain what will happen next in terms of (i) their clinical care and (ii) their research follow-up

This can happen at the patient's home, at the hospital/ clinic, or remotely by telephone/ video communication, as appropriate. If a patient consents to participate during a telephone/ video contact, written consent must be obtained prior to randomisation. If the physical assessment data are collected remotely from electronic records, elements that are not possible to collect remotely can be collected at the next opportunity and recorded in the case report form against that later date.

Patients who decide not to enter the trial will be offered the opportunity to consent to Registry follow up (see Appendix 17.2). They will also be offered the opportunity of taking part in the qualitative research exploring reasons underlying their decision to not take part (see Section 9.3).

If they decide not to take part in any of the above, they will be thanked for their contribution to the study and the research nurse will explain what will happen next in terms of continuing with their normal care. The numbers declining participation and their reasons for non-participation will be captured in a screening log as recommended in CONSORT [43].

If the patient chooses to attend the research site for the research visits, travel costs can be claimed from the local site and reimbursed by the central coordinating site every quarter.

Websites will not be used to identify potentially eligible participants.

Screen failures can be reconsidered at any point if their age, eGFR, co-morbidity or functional status changes or if they wish to reverse an earlier decision not to participate in the trial.

7.2 Consent

Consent will be obtained at each stage in the study, as appropriate for the patient's level of participation, by the patient's consultant, the principal investigator or a research nurse or clinical trials assistant who will be trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

Only patients with the mental capacity to make this decision will be able to enter the trial and the researcher will seek consent once they deem the patient is fully informed about what the RCT participation entails.

Clinical staff and research staff will be alert to any changes suggesting that capacity has been lost and assess a participant's mental capacity to decide to remain in the trial if they suspect this may be lacking. If that assessment confirms that the participant has lost the capacity to decide to continue with the trial, and this is thought likely to represent a long term loss of capacity, the participant will be withdrawn from the trial and follow up as follows:

- They will discontinue the treatment they have been randomised to and return to usual care
- They will be sent no further patient questionnaires to complete
- Their existing data will be retained
- Certain outcomes (the pre-defined secondary outcomes like mortality and days spent in hospital) will continue to be collected through routine data, such as medical records and linkage. Participants will have consented to this when they had capacity at entry to the trial
- Associated consented family members/ friends/ carers will be able to remain in the trial even if the patient they are associated with loses capacity.

4. When a potential participant declines participation in the trial

Patients who are eligible but not willing to be randomised will be asked if they would be willing to take part in an interview to understand the reasons underlying their decision. Research nurses will explain that this interview is to help improve the clarity of information provided about the study. This information will be used to change the way future patients are approached and informed and no pressure will be exerted on patients who have already declined participation to change their mind. Written information will be provided about this qualitative study. If they agree to take part in this and have the mental capacity to do so, the nurse will obtain informed consent from them. They will also be invited to consent to registry follow up (see Appendix 17.2).

5. Family/ friends/ carers

Family/ friends/ carers of participants in the randomised controlled trial will be provided with additional family/ friend/ carer-specific information about the trial outlining:

- The inclusion of carer burden questionnaires
- The possibility that they may be asked by the patient to complete patient questionnaires by proxy, i.e. for the patient if they have capacity but are not able for some other reason
- The possibility that they may be contacted following the death of their loved one to complete a post-bereavement questionnaire about the quality of life of their loved one in the last days and weeks of life, and an interview with the qualitative researcher.

If they agree to take part in this and have the mental capacity to do so, the nurse will obtain informed consent from them using a separate carer consent form.

Participant Information Sheets and Consent forms will be translated into Welsh locally or provided bilingually where this is requested by a participant at a research site.

7.3 The randomisation scheme

All patients who enter the study will be allocated a unique Patient Study Number via the randomisation system. The research nurse will input the information necessary for randomisation,

i.e. site (stratified) and age 65-79 vs 80+ (minimised). Participants will then be randomly allocated 1:1 to the "prepare for responsive management" or "prepare for dialysis" treatment arms stratified by site to ensure a balance in terms of local differences. Minimisation will be used to ensure balance in age (65-79 vs 80+). We will use minimisation with probability weighting of 0.8 in order to reduce predictability.

Randomisation will be done using the BTC Randomisation System, which provides a secure service to generate allocations. This is a validated system. This system will become inactive by the end of 2023 and replaced by another online randomisation system called Sealed Envelope™ (*www.sealedenvelope.com*).

Post-randomisation

The patient (and relatives/ carers) will be informed of their allocated treatment. As community care is an essential element of the intervention, patients will have to consent to their GP being informed about their participation in the trial. Hospital staff will be informed about the study by the research nurse, so that they can answer queries from participants and their relatives.

7.3.1 Blinding

Due to the nature of the intervention, participants and those administering the intervention will not be blinded to group allocation. Two statisticians will support this trial. The senior statistician co-applicant will be blinded throughout the trial and is responsible for writing the SAP and attending TSC meetings. A trial statistician will perform all disaggregated analyses according to a pre-specified statistical analysis plan and will attend closed DMC meetings as required. The remaining members of the study team will remain blinded to aggregate data only.

7.4 Data collection

7.4.1 Baseline data

Demographic, social, clinical, resource use, laboratory and patient/carer reported data will be collected by research nurses during study visits at baseline (following consent and prior to randomisation). Physical assessment will be performed by the research nurse following standard operating procedures. If patient consent is obtained remotely (see 7.1.1. above), the baseline physical assessment can be conducted at another opportunity within the next 12 weeks. No blood or urine tests are required other than those that are being performed as part of routine care.

Table 1 Summary of baseline data collection for the randomised controlled trial

Demographics/social	Age, sex, ethnicity, marital status, education level, distance lived from kidney clinic, alcohol consumption, smoking history.
Clinical	Primary renal disease, date first seen by nephrologist, co-morbidities, dietary restrictions, prescribed medication.
Resource use	Hospital/nursing home/residential home days/hospice days, other hospital outpatient services and primary care & community services in the last 4 months. Help from family, friends & carers in the last week.

Laboratory	Creatinine, urea, albumin, haemoglobin, haematocrit, mean corpuscular volume, sodium, potassium, bicarbonate, corrected calcium, phosphate, intact parathyroid hormone, total cholesterol. (From the date of the study visit or the closest date prior to the study visit.)
Physical assessment	Height, weight, blood pressure, heart rate, waist circumference, timed "get up and go" [38], hand grip strength (Jamar hand dynamometer) [39], WHO performance status. (Details in standard operating procedures.)
Patient reported	EQ-5D-5L [33], POS-S renal [34], ICECAP-O [35]/ICECAP-SCM [36], Multimorbidity Treatment Burden Questionnaire [37]
Relative/carer reported	PACKS impact on carers questionnaire [40]

7.4.2 Trial assessments

Clinical, resource use, laboratory, compliance with the intervention and patient/carer reported data will be collected by research nurses from primary and secondary care clinical notes and during study visits/contacts. The physical assessment will be performed by the research nurse following standard operating procedures. No blood or urine tests are required other than those that will already have been performed as part of routine care.
Study visits/contacts will be 4-monthly (+/- 4 weeks) until withdrawal from the study, death or end of follow up. They will be arranged face-to-face once a year (at home or in clinic) and by telephone/ video communication twice a year (with online, postal or telephone/ video completion of questionnaires). Some patients may prefer planned telephone/video contacts to be face-to-face and this can be recorded on the follow-up CRF.

If a patient/carer questionnaire is not returned, up to 3 reminders will be sent. If a patient becomes too unwell to complete the patient questionnaires, a proxy report from a relative/carer will be accepted. Relatives/carers will be asked to complete their questionnaires at the same time.

If the patient dies, consented relative/carers will be asked to provide a proxy-report for the deceased's quality of life in the last week of life via a bereavement questionnaire.

COVID-19 considerations

The pandemic period was considered to start in March 2020. Considering the clinical and logistical challenges posed by the COVID-19 pandemic, visits/ contacts can be performed face-to-face or replaced by a telephone or video call according to local policy . Missing data from activities which would normally be undertaken at a face to face visit but cannot happen during a telephone or video call, such as collection of physical assessment data, should be collected at a routine clinic appointment. If this also proves not possible, missing data will not constitute a protocol deviation. Where this is the case the reason for the missing data on the CRF will be recorded with a note such as "Unable to collect due to COVID-19".

Table 2 Summary of follow up data collection for the randomised controlled trial

		Follow up 4 monthly[1]		Participant deceased
		Telephone/ video	In person	
Clinical	Co-morbidities, hospital admissions including dates & causes, dialysis access surgery procedures & complications, other surgery, dialysis treatment received, dietary restrictions, prescribed medication, date location & cause of death.	◊	◊	◊
Resource use	Hospital/nursing home/residential home days/hospice days, other hospital outpatient services and primary care & community services in the last 4 months. Help from family, friends & carers in the last week.	◊ / o	◊ / o	o
Laboratory (All pre-dialysis unless otherwise stated for those on dialysis)	Creatinine, urea (pre- and post-dialysis if on haemodialysis), albumin, haemoglobin, haematocrit, mean corpuscular volume, sodium, potassium, bicarbonate, corrected calcium, phosphate, intact parathyroid hormone, total cholesterol. (From the date of the study visit/contact or the closest date prior to the study visit/contact.)	◊	◊	◊
Physical assessment	Weight, blood pressure, heart rate, waist circumference, timed "get up and go" [38], hand grip strength (Jamar hand dynamometer) [39], WHO performance status. (Details will be set out in standard operating procedures.)		◊	
Compliance with trial	Number of home visits by clinical team from renal unit; Number of	◊	◊	◊

	attendances at CKD clinic; Number of telephone/ video contacts from clinical team at renal unit; Number of visits from the palliative care team; Number of telephone/ video contacts from the palliative care team; Advance care agreed; Advance care plan reviewed/updated; Cardiopulmonary resuscitation decision documented; Preferred place of death documented			
Patient reported	EQ-5D-5L [33], POS-S renal [34], ICECAP-O [35]/ICECAP-SCM [36], Multimorbidity Treatment Burden Questionnaire [37]	● / ○[2]	● / ○[2]	○
Relative/carer reported	PACKS impact on carers questionnaire [40], QUALYCARE post-bereavement survey [41]	●	●	●
[1] Two telephone/ video contacts per year and one in person visit per year; [2] If patient too unwell to complete questionnaire. ◊ Research nurse collected ● Directly reported by participant or relative/carer ○ Proxy reported by relative/carer. Considering the clinical and logistical challenges posed by the COVID-19 pandemic, 'in person' follow up can be replaced by a telephone/ video call according to local policy.				

The study visits/contacts of two example patients, one recruited in the first month of recruitment and one recruited in the last month of recruitment, are set out in Table 3.

Table 3 Example research visit/contact schedule for patients recruited in first and last month of recruitment

Visit/contact	1	2	3	4	5	6	7	8	9	0	11	12	13
Month	1	5	9	13	17	21	25	29	33	37	41	45	49
Visit/contact type													
Recruited in July 2017	Jul 17	Nov 17	Mar 18	Jul 18	Nov 18	Mar 19	Jul 19	Nov 19	Mar 20	Jul 20	Nov 20	Mar 21	Jul 21
Recruited in June 2021	Jun 21	Oct 21	Feb 22	Jun 22	Oct 22	Feb 23	Jun 23						

 = In-person study visit (home or hospital/clinic);  = Telephone/ video study contact. Considering the clinical and logistical challenges posed by the COVID-19 pandemic, home visits can be replaced by a telephone or video call according to local policy.

7.4.3 Long term follow-up assessments

At the point of consenting to take part in the RCT, all participants will be asked to consent to linkage to existing healthcare databases, such as Hospital Episode Statistics, the Office for National Statistics and the UK Renal Registry. This will provide data on commencement of acute or chronic dialysis, hospital admissions for medical and surgical reasons and date and cause of death. This will enable follow up of outcomes (though not quality of life) for participants who wish to stop providing data to the study who might otherwise be lost to follow up, including those who move to a renal unit not participating in the trial.

7.5 Withdrawal criteria

Participants can withdraw from (a) complying with the allocated trial treatment or (b) providing data to the trial, at any time for any reason without affecting their usual care. In both cases all efforts ethically appropriate will be made to report the reason for withdrawal as thoroughly as possible on the withdrawal form.

Should a participant wish to withdraw from receiving the allocated trial treatment, efforts will be made to continue to obtain follow-up data, with the permission of the patient or family/ friend/ carer as appropriate. On withdrawal from the trial, the participant will return to usual care as deemed appropriate by their renal unit.

To provide reassurance that continuing with the allocated trial treatment remains clinically appropriate, a set of safety indicators has been agreed (Section 10). If any one of these indicators is reached, the clinical nurse must seek confirmation from the responsible nephrologist that remaining on the allocated treatment remains appropriate.

Patients randomised to prepare for responsive management will also be considered to have withdrawn from their treatment arm if they:

- Have a plan to prepare for dialysis entered in their clinical record (e.g. letter to GP)
- Have a dialysis access procedure (surgery or line insertion) for end-stage kidney disease or commence dialysis for end-stage kidney disease.

Participants randomised to prepare for dialysis will be considered not to comply with their allocated treatment from the date that they:

- Decide, with their responsible nephrologist, that they will not start dialysis in the future, even if they become symptomatic of ESKD, and this decision is documented in the clinical record and in a letter to the GP (i.e. date of entry in clinical record).

7.6 End of trial

The sponsor will notify the main research ethics committee of the end of a trial within 90 days of its completion, i.e. the date of the last visit/data item of the last patient undergoing the trial.

7.7 Assessment of compliance

Process evaluations will be used to study how the intervention is implemented and may provide information on contextual factors that affect the intervention. They will also provide us with information in this multi-site trial about the uniformity of delivery of the intervention, where the "same" intervention may be implemented and received in different ways. Stage 3 of the integrated qualitative research will provide a more in-depth understanding of how the trial treatments and procedures are being delivered in practice (see Section 9.4).

Process information will be documented in the electronic Clinical Team Activity Record (CTAR). The CTAR will be used every time there is a contact with a patient or carer or healthcare professional. This will record the nature and length of the contact.

The research nurse will use the CTAR alongside the clinical notes to capture delivery of components of the conservative care intervention to patients in both arms of the trial in a dedicated section in the follow up CRF. From here compliance can be reported to the DMC and Sponsor.

Where a patient misses more than 2 consecutive monthly calls the research or clinical nurse will try to speak to the patient and/ or their carer to understand the reasons for missing the calls. This may be by telephone, video call or email or when attending a hospital appointment. If, after a further 2 months, no contact has been established with the patient a REC approved letter and reply slip asking patient to confirm their wish to remain in the study. A non-response will be considered a wish to withdraw from the study.

The primary analysis will be intention to treat. For this reason, even if a patient is documented as deviating from protocol or withdrawing from their randomised treatment, they will be encouraged to continue with study visits/contacts and patient questionnaires.

Participants randomised to prepare for responsive management will be considered non-compliant with their allocated treatment from:

- 90 days after randomisation, if they have received none of their “Assess” visits by this time.
- The date of the annual research face-to-face review (which can be undertaken remotely, if clinically indicated), if they are found at that visit/ contact to have received responsive management clinical contact in 7 or fewer calendar months in preceding year. For this purpose, responsive management clinical contact is defined as a clinic visit, a telephone/ video call, or a home visit where the patient or their representative is seen or spoken to, or the patient has left a message (e.g. in response to a missed clinic or call) saying that they have no medical issues needing responsive management.

Sensitivity analyses will involve studying how many patients in each arm stop complying with their allocated treatment by either deciding not to start dialysis (participants randomised to prepare for dialysis) or deciding to undergo a dialysis access procedure (participants randomised to prepare for responsive management). We will explore the timing of the move, reason for not complying with treatment (where data are available) and the characteristics of patients making this decision.

8. TRIAL INTERVENTION - THE ‘PREPARE FOR RESPONSIVE MANAGEMENT’ PATHWAY

Following allocation of the participant to the prepare for responsive management arm, the research nurse will inform the patient and their family/ friend/ carer about what will happen thereafter in terms of (1) responsive management visits/contacts and (2) research team visits/ contacts.

8.1 Assess

The participant will receive their first telephone/ video contact from a healthcare professional delivering the responsive management package within 2 weeks of referral i.e., being informed of the patient’s randomised allocation by the research team.

The date contact is made and the duration of this telephone/ video contact will be documented. This first contact will cover:

- Initial introductions; explain role of team; review symptoms and concerns of patient and, if appropriate, family/ friend/ carer; limited telephone/ video responsive management assessment.
- Agree date and time for first visit/contact. Location should be patient’s home. Visit can be done at another location (e.g. hospital if patient is attending outpatient clinic or elsewhere) if there are concerns about safety or if patient prefers, but this should be exceptional.
- as mutually agreed.

The healthcare professional will then consult with colleagues in the rest of the renal team and contact with any other relevant professionals (e.g. palliative care, primary care, rehabilitation) as required for background information. At least one and up to 3 visits/contacts can be conducted for the ‘Assess’ stage of Responsive Management.

Visit 1

The participant will receive their first visit from a healthcare professional delivering the responsive management package within 3 weeks of first telephone/ video contact.

The date and duration of this visit will be documented on the CTAR.

A comprehensive advanced CKD care assessment will be carried out and documented. This will cover:

- Completion of symptom checklist (iPOS-S renal or equivalent)
- Symptom control and management
- Continuity and co-ordination of care, access to services
- Psychosocial needs
- Information/communication needs
- Advance care planning
- Assessment of caregiver

This will generate an agreed personalised problem list and action plan including agreement of plan for next visit/contact.

The patient and their family/ friend/ carer will be given information about the responsive management package and given contact details for the healthcare professionals delivering the responsive management package.

After visit 1

- The patient's case will be discussed with the multi-disciplinary team (including their named consultant nephrologist and GP) and these discussions documented. When complete, this will be sent to the patient and all relevant health professionals.
- The problem list/plan from first visit will be reviewed with multi-disciplinary team the healthcare professional will liaise with relevant health, social and voluntary sector professionals to ensure other services are provided and other needs met.
- A decision will be made whether a further home visit is required. (It is anticipated that the majority of patients will need two home visits.)
- The patient and their family/ friend/ carer will be contacted as agreed in the plan and as required. All contacts made with the patient/carer or with healthcare professionals outside the study visits will be documented.
- The date and time of the second visit will be confirmed, if required.

Visit/ Contact 2

If required, the second visit from the healthcare professional delivering the responsive management package will take place within 6 weeks of Visit 1. The date and duration of this visit will be documented on the CTAR. The second visit/contact can also be delivered remotely.

A comprehensive advanced CKD care assessment will be carried out including:

- A review of outcomes from actions already taken.
- A reassessment of the patient's situation covering the same areas as visit 1.
- A review the personalised advance care plan and any actions as necessary.

After Visit/ Contact 2

- The healthcare professional will liaise with relevant healthcare professionals and provide information, education, advice and co-ordination as required. They will re-review the personalised problem list/plan with multi-disciplinary team and record all activity. When complete, they will communicate the plan with the patient and all relevant health professionals.
- The healthcare professional will contact the patient and their family/ friend/ carer as agreed in plan and as required. All contacts made with the patient/carer or with healthcare professionals in relation to the patient outside the study visits will be documented.
- A decision will be made whether a further home visit/ telephone or video contact is required.
- The date and time of the third visit will be confirmed, if required.

Visit/ Contact 3

If required, the third visit from the healthcare professional delivering the conservative care package will take place within 6 weeks of Visit 2. The date and duration of this visit will be documented on the CTAR.

A comprehensive advanced CKD care assessment will be carried out, including:

- A review of outcomes from actions already taken.
- A reassessment of the patient's situation covering the same areas as visit 2.
- A review the personalised advance care plan and any actions as necessary.
- The first of monthly telephone/ video contacts will be arranged.

Considering the clinical and logistical challenges posed by the COVID-19 pandemic, these assess visits/ contacts can be performed face-to-face or replaced by a telephone/ video call should local policy require.

8.2. Responsive Management

8.2.1 Routine Support

Annual review from healthcare professional delivering the responsive management package

These will take place every 12 months on the anniversary of the final 'Assess' visit/ contact (+/- 8 weeks) to reassess the patient's needs and priorities for care in their home environment. This will ideally to be done in the person's own home with friends/ family members present, but can be done by telephone or video call if this is requested by the patient or deemed more appropriate for clinical reasons. To achieve this, they will include a comprehensive advanced CKD care assessment (for more detail see section 8.1):

- Completion of symptom checklist (iPOS-S renal or equivalent)
- Symptom control and management
- Continuity and co-ordination of care, access to services
- Psychosocial needs
- Information/communication needs

- Advance care planning
- Assessment of caregiver

This will generate and regularly review an agreed personalised problem list and action plan including agreement of plan for next visit/contact. The visit and plan will be discussed and agreed with the MDT. If despite optimisation of their medication the patient's symptoms are proving difficult to adequately control and the patient still wishes to follow a responsive management pathway, treatment will escalate to "Supportive care" (see Section 8.3 below).

Clinic visits with the patient's consultant nephrologist

The patient's named consultant nephrologist will not change as a result of taking part in this trial. Clinic visits should continue as per routine practice with one clinic visit being replaced with an annual home visit from the healthcare professional delivering the responsive management package. For example, if the patient is being seen every 3-4 months in clinic prior to entry into the trial they will continue to be seen in clinic every 3-4 months, but one of these visits will be replaced by a home visit from a healthcare professional annually.

The content of these clinic visits will be determined by the treating nephrologist but should not include preparation for dialysis unless the patient decides to withdraw from the responsive management pathway. In this situation, the research team should be informed as soon as possible, optimally within 1 week of the clinic visit.

It may be appropriate, for example if the patient becomes particularly frail, for some of the clinic visits to be replaced with GP visits. If this is the case, the GP will be liaising with the treating nephrologist for specialist advice and the monthly telephone/ video calls and home visits from the clinical nurse will continue at the same frequency.

Considering the clinical and logistical challenges posed by the COVID-19 pandemic, these routine support home visits and clinic visits can be performed face-to-face or replaced by a telephone/ video call according to local policy.

Monthly telephone/ video contacts

These telephone/ video contacts will consist of an abridged advanced CKD care assessment, including:

- Completion of symptom checklist (iPOS-S renal or equivalent)
- Changes to medication to optimise symptom control
- Information/communication needs

Telephone/ video contacts should occur once in each calendar month in which there is not a clinic visit or home visit. The ideal will be regular intervals between calls wherever possible but some patients may express a desire to reduce this frequency but remain on study if they are well or find it surplus to requirements at that time. All actions will be documented.

At each telephone/ video contact, the health professional will compare current responses with previous responses looking for any worsening of symptoms and if present:

- Review symptoms and treatment with the MDT and make any possible changes to medication to control symptoms
- If clinically appropriate, arrange face-to-face contact either through a home visit or a clinic visit or a community team visit

If despite optimisation of their medication the patient's symptoms are proving difficult to adequately control and the patient still wishes to follow a conservative care pathway, treatment will escalate to "Supportive care" (see Section 8.3 below).

8.2.2 Responsive Support

In response to each individual patient's evolving personal, social and clinical situation, a range of options will be available to ensure that the patient feels as supported and safe as possible in their preferred place of care. The option chosen will depend on the individual scenario and the clinical assessment of the most locally appropriate way to respond, but could include:

- Supporting the patient at home: telephone/ video calls from the renal unit team, community team or GP; appointments at the GP surgery, and; home visits from the renal unit team, community team or GP.
- Supporting the patient up to the hospital/ clinic: renal outpatient clinic visits; palliative care outpatient clinic visits, and; admission to hospital or the hospice, if required.

8.3. Supportive care

If the patient develops symptoms of advanced CKD that cannot be adequately controlled, they should progress to the "Supportive care" stage. This transition may occur at a monthly telephone/ video contact or face-to-face visit or between contacts, for example during an inter-current illness.

The Advance Care Plan and any other documentation relating to priorities for care must be reviewed and the appropriate local community and palliative care services activated and coordinated to achieve good end-of-life care. This must be done rapidly to prevent inappropriate default "cure-centred" care being administered in the event of a sudden deterioration.

In principle, the package of care should aim to deliver the following five patient priorities for quality end-of-life care [44]:

- Receiving adequate pain and symptom management
- Avoiding inappropriate prolongation of dying
- Achieving a sense of control
- Relieving burden on loved ones
- Strengthening relationships with loved ones

We recognise that each renal team is likely to have their own prescribing guidance for pain and symptom management at the end of life in advanced CKD, but guidance has also been published that some may find helpful and this will be shared with the teams.

Although the renal unit team may want to continue to lead at this stage of care, it is often more appropriate to hand over day-to-day management to the local community teams – palliative care and general practice. If earlier stages of the conservative care package have worked effectively, these services will already be aware of the patient and the possibility that they may need end-of-life support. Written and telephone/ video guidance on prescribing in advanced CKD is generally welcomed by these teams, who may be unfamiliar with the appropriate drugs and doses to use in end-stage kidney disease.

The timelines described in Section 8 are guidance to provide a framework against which to work and are not mandatory schedules. Protocol deviations / non-compliances are defined in section 7.7.

9 QUALITATIVE ASSESSMENTS-NESTED STUDIES

9.1 Overview of qualitative research integrated throughout study

Qualitative and mixed-methods research will be integrated throughout Prepare for Kidney Care to address key objectives at different stages of the RCT. The objective of Stage 1 (months 0-6) is to optimise the trial design prior to initiation of the pilot RCT. Stage 2 will implement the 'QuinteT recruitment intervention' (QRI) with the aim of optimising trial recruitment processes during the pilot stage (months 6-30). The aim of stage 3 (month 12- 54) is to investigate the adherence and acceptability of the trial comparison groups (and processes) to patients and the professionals involved in their care.

9.2 Stage 1: Optimising trial design

Qualitative research at the pre-trial stage can optimise the efficiency of RCT processes and enhance the relevance and acceptability of trial design [45, 46]. The first draft of the Prepare for Kidney Care protocol was designed with patient and clinician input and underwent extensive peer review through the funding acquisition process. There is, however, a need to present the RCT protocol to stakeholders anticipated to deliver the RCT.

9.2.1 Aim and objectives

Stage 1 of the integrated qualitative study aims to understand key stakeholders' perspectives on the proposed RCT with a view to refining the protocol. This work will be carried out in advance of the formal start date of the RCT (i.e. prior to sites formally opening and enrolling patients). The main objectives of stage 1 are to understand:

a) Clinical professionals' perceived acceptability of the proposed trial interventions.
b) Clinical professionals' perceptions of equipoise, particularly in relation to the proposed eligibility criteria.
c) Trialists' and professionals' views about the barriers and facilitators of delivering the RCT in the context of local health care systems.

Findings from interviews will be summarised in a report for the CI and fed back to the TMG to finalise decisions about: a) details of the intervention; b) the trial eligibility criteria, and c) trial recruitment processes. A clinical consensus meeting will be held towards the end of stage 1, with the aim of finalising these decisions.

9.2.2 Design

Stage 1 will consist of qualitative, semi-structured interviews with NHS health care professionals who are anticipated to be involved in supporting or delivering the forthcoming RCT. Semi-structured interviewing has been selected as the main route of enquiry, as these allow key topics of interest to be covered within a flexible framework that provides opportunities for new themes to emerge (i.e. issues that might not have been anticipated by the researchers).

9.2.3 Sampling and recruitment

Stage 1 of the qualitative research will be conducted across the sites participating in the internal pilot phase of the Prepare for Kidney Care study:

- North Bristol NHS Trust
- Heart of England NHS Foundation Trust, Birmingham
- Royal Stoke University Hospital (University Hospitals of North Midlands Trust), Stoke-on-Trent
- The Royal Free London NHS Foundation Trust
- The Lister Hospital (East and North Herts NHS Foundation Trust), Stevenage
- Gloucestershire Royal Hospital, Gloucester

Sampling of potential interview participants will be purposeful, guided by intentions to recruit 'key informants'. A key informant in the context of this study will be defined as any individual responsible for delivering care to the eligible patient population, or any individual who has a role in delivering the trial.

Key informants will be identified at site initiation meetings and through liaison with the trial management group (e.g. the trial manager and trial coordinator, who will have links with the research teams at each site). The qualitative researcher will attempt to attend as many site initiation meetings as possible (depending on practical constraints). Snowball sampling techniques will also be employed, where interview participants suggest other individuals deemed appropriate to approach (in accordance with the objectives of the stage 1 qualitative interviews). As data collection progresses, further sampling will be guided by intentions to develop emerging themes or theories. Sampling will continue until the research team are confident that they have reached 'data saturation' – defined as the point at which no new themes emerge from three consecutive interviews.

Potential participants will be sent invitation letters and study information sheets explaining the study via post and/or email, prior to any discussions about interviews, to enable adequate time to read the information sheet. They will be asked to express interest to participate by contacting the named qualitative researcher via e-mail, telephone/ video, or a reply slip attached to their invitation letter (to be returned in a pre-paid envelope). This slip will also provide an option for individuals who do not wish to take part in the research. The letter will request potential participants to indicate if they do not wish to participate, as this will alert the qualitative researcher to make no further contact. Participants will be asked to respond to the invitation letter within two weeks. Those who do not respond will be sent reminders (another invitation letter and participant information sheet). Any late respondents will still be eligible for participation, as long as the project is ongoing.

9.2.4 Data collection and consent processes for stage 1

Interviews will be conducted face-to-face or via telephone/ video. Face-to-face interviews are likely to be in a private room within a professional healthcare organisation or the research base (University of Bristol). Interviews will be up to one hour in duration and will be audio-recorded (subject to relevant permissions on the consent form). A topic guide will be used to ensure key topics are consistently covered across interviews. It is anticipated that this topic guide will evolve as new themes emerge through continued data collection. The qualitative researcher will obtain informed consent on the day of the interview.

9.3 Stage 2: Quintet Recruitment Intervention (QRI) to optimise recruitment and informed consent (months 6-30)

The QRI aims to optimise recruitment and informed consent in the Prepare for Kidney Care study [47] , and will begin as soon as the first centres officially open to recruitment. Recruitment may be challenging in relation to the identification of potentially eligible patients and differences in levels of equipoise. The QRI will attempt to identify sources of recruitment difficulties and implement interventions to address these throughout the recruitment period. This work will be intensively conducted in clinical centres in the internal pilot phase. Lessons learnt from the QRI will subsequently be applied to other centres, combined with continued investigation of recruitment challenges as they occur. The process will assimilate investigation of generic and centre-specific recruitment challenges, with a combination of pre-emptive and responsive feedback/training.

The QRI uses novel qualitative and mixed-method approaches pioneered during the HTA-funded ProtecT (Prostate testing for cancer and Treatment) study [48]. These methods have since been refined and applied to several other RCTs in different clinical contexts, all of which have led to insights about recruitment issues and the development of targeted recruitment strategies [31]. The QRI will proceed in two iterative phases: a detailed understanding of the recruitment process will be developed in phase I, leading to tailored interventions to improve recruitment in phase II.

9.3.1 Data collection methods for the QRI

Phase I: understanding recruitment issues

Phase I will focus on building up a comprehensive understanding of recruitment challenges that arise during the pilot RCT. A multi-faceted, flexible approach will be adopted, using one or more of the following methods:

a) Mapping patient eligibility and recruitment pathways: Detailed eligibility and recruitment pathways will be compiled for clinical centres, noting the point at which patients receive information about the trial, which members of the clinical team they meet, and the timing and frequency of appointments. Recruitment pathways will be compared with details specified in the trial protocol and pathways from other centres to identify practices that are potentially more/less efficient. The qualitative researcher will also work closely with the CTU to compose detailed logs of potential RCT participants as they proceed through screening and eligibility phases, to help identify points at which patients do not continue with recruitment to the RCT. Logs of eligible and recruited patients will be assembled using simple flow charts and counts to display numbers and percentages of patients at

each stage of the eligibility and recruitment processes. These figures will be compared across centres, and considered in relation to estimates specified in the grant application/study protocol.

b) Audio recording and observation of recruitment appointments: Scheduled appointments and/or home visits during which the trial is discussed will be audio-recorded and/or observed with permission, including conversations carried out remotely. All staff involved in discussing Prepare for Kidney Care with patients will be invited to record their discussions with patients using an encrypted platform of choice. The recordings will be used to explore information provision, recruitment techniques, management of patient treatment preferences, and randomisation decisions to identify recruitment difficulties and improve information provision. Recordings will be transferred to and from the University of Bristol (for analysis) through University of Bristol-approved secure data transfer facilities and/or encrypted flash drives that adhere to NHS Trust policies.

c) Semi-structured Interviews may be conducted with:

- Members of the TMG, including the CI and those closely involved in the design, management, leadership and coordination of the trial.
- Clinical and recruitment staff across all centres delivering the RCT.
- Eligible patients who are approached to take part in the RCT.

Interviews with TMG members/recruiters will investigate their perspectives on the RCT and experiences of recruitment (where relevant). Key topics explored will include views about the trial design and protocol; understandings of the evidence on which the trial is based; perceptions of uncertainty/equipoise in relation to the RCT arms; views about how the arms/protocol are delivered in clinical centres; methods for identifying eligible patients; views on eligibility, and examples of actual recruitment successes and difficulties.

Interviews with patients will explore views on the presentation of study information, understandings of trial processes (e.g. randomisation), and reasons underlying decisions to accept or decline the trial. Patients will be purposefully selected, to build a sample of maximum variation on the basis of age, multi-morbidity status, gender, study centre, and the final decision about trial participation (i.e. accept or decline). Numbers of interviews will be guided by the concept of 'data saturation' – the need to continue sampling until findings become repetitious.

QRI interviews will take place at a mutually convenient location, in a suitably private and quiet setting. All participants will be offered the option to conduct the interview over the telephone or a secure audio-visual platform. The University of Bristol's 'lone researcher' safety policies will be upheld for any interviews taking place in non-public settings (e.g. participants' homes).

d) Observation of TMG and investigator meetings: It is likely that the CI, TMG and clinical investigators will meet or have telephone/ video conferences to discuss the progress of the RCT. The qualitative researcher will observe and potentially record these meetings, with permission. The aim will be to gather further information about specific issues that may have a bearing on recruitment. These meetings can also elucidate new solutions to recruitment difficulties.

e) Document analysis of trial materials: PILs, the study protocol, and other trial literature will be scrutinised to identify aspects that are unclear or potentially open to misinterpretation, thus having a possible bearing on recruitment.

Phase 2: Development and implementation of recruitment strategies

Findings from Phase 1 will be presented to the CI and TMG (with permission from CI). If recruitment difficulties are evident across the study or in particular centres, the CI/TMG and QRI team will formulate a 'plan of action' to improve recruitment and information provision. The specific plan implemented will be grounded in the findings from phase 1, with its format dependent on the nature of the recruitment barriers identified. For instance, generic challenges such as how to explain trial processes (e.g. randomisation) may be addressed through dissemination of 'tips and guidance' documents. Supportive feedback will be a core component of the plan of action, with the exact nature and timing dependent on the issues that arise. Centre-specific feedback may cover institutional barriers, while multi-centre group feedback sessions may address widespread challenges that would benefit from discussion. All group feedback sessions will be aided by anonymised data extracts from interviews and recorded appointments. Individual confidential feedback will also be offered – particularly where recruiters experience specific difficulties or where there is a need to discuss potentially sensitive issues. Investigator meetings and site visits (conducted in person or remotely) may also be employed to discuss technical or clinical challenges (e.g. discomfort surrounding eligibility criteria).

Iterative nature of Phases 1 and 2

The QRI has been presented as two distinct phases for clarity, although in reality these are likely to overlap or run in tandem. For instance, new avenues of enquiry may emerge through feedback meetings, which can be a route to investigating recruitment difficulties in their own right. Insights into recruitment can emerge at any point during the RCT and instigate further investigations (phase 1) or intervention (phase 2).

Evaluating changes in recruitment practice and randomisation

The impact of QRI interventions implemented in phase 2 will be evaluated through mixed approaches, including 'before/after' comparisons (number of recruited patients, eligible patients identified, patients accepting allocation) and investigation of changes in recruiter practice (through continued analysis of recorded appointments). Semi-structured interviews will be conducted with recruiting staff and TMG members to explore their views on QRI interventions and suggestions for areas that would benefit from continued QRI input.

9.3.2 Consent processes for the QRI

Health care professional consent

Recruiting staff and TMG member consent will be obtained through a 'master' consent form that covers all aspects of the qualitative research throughout stage 2 (the QRI) and stage 3 (described in next section); this form sets out individual clauses for each aspect of the qualitative research, with the option to select 'Yes' or 'No' for each research activity accordingly. Research nurses or the qualitative researcher will obtain written consent from all staff. We will also employ a verbal consent process to reduce burden on health care professional participants, where obtaining consent in person is problematic (e.g. due to lack of research nurse capacity, infection control precautions). The QRI researcher will call the healthcare professional and read each statement on the consent form, initial these as is appropriate, and sign to confirm they have obtained consent. The consent discussion will be recorded and a copy of the completed form will be sent to the participant for their

records. This will be a one-off process to cover consent for all future recordings of appointments, interviews, and observations of TMG/investigator meetings throughout the study.

Patient consent

*Recording/observing recruitment appointments***:** Patient consent for recording/ observing appointments will be a two-step process. Recruiters will obtain verbal consent to record the discussion when they first contact the potential Prepare for Kidney Care participant. Patients will receive the QRI patient PIL during this appointment or via post (if conducted over the phone), and will be provided with sufficient time to read the information, ask any questions, and consider their participation. Patients who agree to their appointments being recorded/ observed will sign a written QRI consent form or give verbal consent during a subsequent contact carried out by the research nurse. Future discussions will be recorded subject to obtaining consent; if patients choose not to consent to their appointments being recorded, the recording made from their initial recruitment appointment will be deleted and no further recordings made.

Interviews: The QRI consent form will include a clause that asks patients if they would be willing to be take part in a future research interview ('Yes' or 'No'). Patients who select 'Yes' may then be approached by the qualitative researcher.

9.4 Stage 3: Evaluation of trial processes/interventions and adherence to allocated treatment (months 12-54)

Stage 3 of the integrated qualitative research has two objectives: a) to explore the acceptability of the intervention and trial processes, and b) to understand reasons for non-compliance/protocol deviations. This stage will begin shortly after recruitment initiates and continue into the follow up phase of the study.

There will be an intention to interview trial participants (and/or family members/ friends/ carers) within the first year of randomisation, with follow up interviews arranged at regular (but flexible) intervals to construct longitudinal summaries of experiences of patients (and family member/ friends/ carers). The exact frequency and timing of subsequent interviews will vary depending on clinical events and patient and their family member/ friend/ carer preferences, but it is anticipated that at least one follow up interview will be conducted each year. In addition to the above, patients who decide to discontinue trial treatment and withdraw from the RCT (and/or their family members/ friends/ carers) will be invited to take part in a specific interview that explores the reasons underlying these events. Other health care professionals involved in patient care/decision making will also be targeted for interview (e.g. nurses, GPs, renal consultants, and palliative care specialists).

Interviews that explore acceptability and adherence will be supported with observational data of how the protocol is being implemented in practice. Nurse follow up visits and telephone/ video discussions with patients will be observed and recorded (with informed consent being obtained) to understand the content and nature of these appointments and any difficulties in implementing the intervention or trial processes.

In addition to the above, the acceptability of trial processes and end-of-life care will be specifically explored with family members/ friends/ carers of deceased patients. These individuals will be informed about the possibility of being contacted for interview in the 'carer-specific PIL', distributed at the consent stage for the RCT (see Section 9.3.2, above).

9.4.1 Sampling

All patients who consent to taking part in the trial will be eligible for the stage 3 qualitative study. Sampling will be purposeful, with an intention to build a sample of maximum variation, reflecting the full range of quality of life scores reported, and a range of patients with clinical characteristics at the extremes of eligibility criteria (on trial entry). Patients will be approached for interview at multiple time points from the point of randomisation, with a view to constructing longitudinal summaries of their experiences and how these vary over time.

9.4.2 Consent processes

See Appendix 4 for a flow diagram of when consent is taken for the different stages of the main trial and the nested qualitative study.

9.5 Qualitative analysis

All qualitative interviews and recruitment discussions will be recorded using digital encrypted recorders, and transcribed verbatim by an approved transcription services that has the necessary signed confidentiality agreements with the UoB. All transcripts will be edited to ensure anonymity of respondent. Data will be managed using NVivo software, and stored on encrypted drives at the UoB in line with the university's data storage policies.

Interviews conducted throughout the trial will be thematically analysed using constant comparative approaches. Case study approaches will also be used to analyse data from patients interviewed at multiple time points (for interviews focusing on patient acceptability of interventions), and patients for whom there is potential to combine interview with observational data. A sample of transcripts from each set of interviews will be independently coded by a second qualitative methodologist. A basic coding frame will be agreed, though this is anticipated to evolve as data collection proceeds for each set of interviews. There will be an attempt to search for negative cases in relation to particular themes. Descriptive accounts of emerging interview findings will be prepared throughout the process of analysis for each set of interviews. These documents will evolve as analyses progress and discussions amongst the research team develop over time.

Recorded recruitment consultations and follow up discussions will be subjected to content, thematic, and novel analytical approaches, including targeted conversation analysis [49] and appointment timing (the 'Q-Qat method') [50]. There will be a focus on aspects of information provision that are unclear, disrupted, or potentially detrimental to recruitment and/or adherence. Notes from observations of appointments and TMG/investigator meetings will be documented in a detailed log for each qualitative program of study. Key issues/themes from these notes will be considered alongside emerging findings from interviews and recorded appointments.

10. SAFETY

10.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

10.2 Safety monitoring

Due to the nature of advanced CKD and its treatment, especially in multi-morbid frail older people, SAEs would be expected to occur frequently throughout the course of the disease. These expected SAEs include:

- Abnormal electrolyte and haematological laboratory results that can be explained directly or indirectly by their advanced CKD
- Hospital admissions – elective and emergency – that can be explained directly or indirectly by their advanced CKD
- Hospice admissions – planned and emergency – that can be explained directly or indirectly by their advanced CKD
- Infections and cardiovascular events that can be explained directly or indirectly by their advanced CKD
- Commencement of dialysis
- Death that can be explained directly or indirectly by their advanced CKD

Given the high frequency of SAEs expected, the intensive monitoring of CKD patients in usual care, and the routine use of dialysis and conservative care in the NHS, the Prepare4KC trial utilises the following risk-adapted safety reporting approach:

1. All serious adverse events (hospital admissions and deaths) are collected as part of the study data on the trial CRFs, including an assessment of expectedness and relatedness by the site. These will be regularly reviewed by the study team, and the Data Monitoring Committee.
2. Only SAEs categorised as unexpected and causally related to the intervention require expedited reporting. These SAEs must be reported on the SAE form to the CI and the sponsor as described under section 10.3 below.

10.3 Recording and reporting of SAEs

All reportable (related and unexpected) SAEs occurring from the time of consent until 30 days after the end of the trial must be documented on the SAE form (see Key Trial Contacts section for link to website) and emailed securely to the CTU within 24 hours of the research staff becoming aware. The CI will notify the Research Ethics Committee and the Sponsor within 15 days of becoming aware of the event.

For each reportable SAE the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial/intervention), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

Each reportable SAE must be reported separately and not combined on one SAE form. Any change of condition or other follow-up information relating to a previously reported SAE should documented on the appropriate form (see Key Trial Contacts section for link to website) and emailed securely to the CTU as soon as it is available or within at least 15 days of the information becoming available to the research team. Events will be followed up until the event has resolved or a final outcome has been reached.

Other relevant adverse events which are not defined as serious will be captured as part of the primary and secondary outcomes for the trial.

10.4 Responsibilities

Adverse events will be documented and reported in accordance with North Bristol NHS Trust's Safety Reporting SOP.

10.4.1 Principal Investigator/research nurse

Principal investigators (PIs) and research nurses at each site will be checking for AEs when participants attend for treatment /follow-up; they will be responsible for:

- Using medical judgement in assigning seriousness, causality and expectedness.
- Ensuring that all related and unexpected SAEs are documented and reported to the CTU within 24 hours of becoming aware of the event and provide further follow-up

information as soon as available. Ensuring that SAEs are chased with the CTU if a record of receipt is not received within 2 working days of initial reporting.
- Ensuring that SAEs are documented and reported to the CTU in line with the requirements of the protocol.

10.4.2 Chief Investigator

The chief investigator will be responsible for:

- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit.
- Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
- Using medical judgement in assigning expectedness.
- Immediate review of all reportable SAEs.
- Ensuring safety reports are prepared in collaboration with appropriate members of the TMG group for the main REC and DMC.
- Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk/benefit.
- Reporting safety information to the independent oversight committees identified for the trial (DMC and TSC).
- Expedited reporting of related and unexpected SAEs to the REC within required timelines.
- Notifying PIs of SAEs that occur within the trial.
- Central data collection of SAEs.

10.4.3 Sponsor

The sponsor will be responsible for:

- Overall oversight of the trial.

10.4.4 Trial Steering Committee (TSC)

In accordance with the Trial Terms of Reference for the TSC, this group will be responsible for periodically reviewing safety data and liaising with the DMC regarding safety issues.

10.4.5 Data Monitoring Committee (DMC)

In accordance with the Trial Terms of Reference for the DMC, this group will be responsible for periodically reviewing unblinded overall safety data to determine patterns and trends of events, or identifying safety issues, which would not be apparent on an individual case basis.

10.5 Symptoms, results or events that should trigger senior clinical review

Although all clinical teams will have their own local arrangements for seeking senior clinical review of a patient about whom they have concerns, it is necessary for the safe delivery of the intervention to agree a minimum threshold across all sites for making the patient's nephrologist aware of any change in the status of their kidney condition. Such causes for concern fall into a number of categories:

Symptoms

- Any severe or overwhelming symptoms on the iPOS-S renal or equivalent (see Key Trial Contacts section for link to website) reported for the first time during planned or unplanned telephone/ video or face-to-face healthcare professional contact

Blood results

- An eGFR below 6 mL/min/1.73m^2
- A potassium above 6.5 mmol/L
- A urea above 40 mmol/L

Events

- An unplanned GP/emergency department/hospital attendance due to fluid overload
- An unplanned GP/emergency department/hospital attendance due to infection causing systemic illnesses

Other

- Concern about unexplained or rapid loss of flesh weight (i.e. after allowing for changes in weight due to removal of fluid)
- The patient or their family/ friend/ carer is expressing doubts about the appropriateness of them continuing on the allocated treatment that cannot be resolved
- The healthcare professional believes that a senior clinical review is required

In the event of the healthcare professional delivering the intervention becoming aware of any of the above, they must inform the patient's nephrologist (or covering nephrologist) and the research team within 1 working day. Appropriate clinical action should already have been taken by the responsible clinical team, so the purpose of this escalation is to ensure that it remains appropriate for the patient to remain in the trial on their allocated treatment arm.

11 STATISTICS AND DATA ANALYSIS

11.1 Sample size calculation

The total sample size of 512 will have 90% power to detect a difference between the pathways of 0.345 QALYs (5% two-sided) over 3 years of follow up based on EQ-5D-5L. A discrete choice experiment in 8 renal units in Australia suggests that patients with kidney failure are willing to forgo 7 months of life expectancy to reduce the number of visits to hospital for dialysis by one per week [32]. Responsive management reduces visits to hospital completely. Based on a median EQ-5D utility value for being alive on dialysis of 0.69 [51], 7 months of life at this value would equate to 0.4 QALYs. We wanted to be able to detect a slightly smaller difference than this of 6 months between the two pathways, equivalent to 0.345 QALYs.

For the purposes of informing our calculation we examined data from a longitudinal study [15] of patients that were pre-dialysis where utility score data were available at multiple points during follow up. In that particular study, patients were followed up from eGFR 20-30 ml/min/1.73m^2 until starting dialysis. From these data we calculated total QALYs over 3 years of follow up (based on EQ-5D). The data suggested a bimodal distribution (means 0.36 and 2.4).

Bi-modal distributions of EQ-5D values (which are used to calculate QALYs) have been noted in a variety of conditions including rheumatoid arthritis [52] and cancer [53]. Explanations for such

distributions include the algorithm used to calculate the EQ-5D score itself which tends to cluster scores in the extremity close to 1.0 (perfect health) and near 0.45 (representing moderate health) [54]. While we cannot exclude the possibility that a larger sample would have yielded a unimodal distribution, it is worth noting that a large study of over 1041 Finnish patients with rheumatoid arthritis found a bi-modal distribution for EQ-5D scores [55].

Based on summary statistics from the observed data and visual inspection of the histogram, we simulated datasets of 1,000,000 observations for control groups using the SKBIM command in STATA [56]. This command allows the user to simulate a bimodal distribution while specifying different characteristics of the distribution including means, standard deviations, skewness and kurtosis (for the control group the simulated dataset was generated with this command: skbim (0.5 0.359 0.096 2.413 2.413 0.154 1 1000000 123 0.804 2.492 0 3). To simulate the distribution of QALYs in the intervention group we assumed the same distribution as the control group, but shifted the two means by 0.345 QALYs to reflect a clinically meaningful difference we want to be able to detect. Simulated values greater than 3 were discarded.

Sample size calculations involved re-sampling (1,000 iterations) samples of varying sizes from these simulated distributions of continuous QALY scores and performing Mann Whitney tests. To allow for possible cross over, we selected our intervention group samples by taking 95% of our sample from the intervention distribution and 5% from the control distribution. The same process was used to identify the control group sample.

Having 230 patients/group allows detection of a difference between the pathways of 0.345 QALYs with 90% power (2-sided a=0.05). As death is not a censoring event (utility becomes and remains 0) so loss to follow up should not exceed 10%. Allowing for loss-to-follow-up increased the total sample size to 512.

11.2 Planned recruitment rate

Based on numbers of patients starting renal replacement therapy it is estimated that there will be ~270 patients aged 65+ with an eGFR less than 15mL/min/1.73m^2 in each renal unit over the recruitment period of the trial. Considering the co-morbidity, performance status and the additional age criteria, we estimate that 40% of these patients will be eligible (~20% will have 3+ co-morbidities (1, 2), 15-25% will have a dependent performance status (1, 53) and ~30% will be over 80 years (54)). This gives an estimate of 108 eligible patients per renal unit over the recruitment period of the trial. If we assume 20% of these agree to participate in the first 6 months in each site, increasing to 33% after this with the embedded QRI, we estimate that with 16 sites we will recruit 512 patients by month 30, equivalent to 1.7 per site month.

11.3 Statistical analysis plan

11.3.1 Summary of baseline data and flow of patients

Analysis and reporting will be in line with CONSORT guidelines and the primary statistical analyses will be conducted on an intention-to-treat (ITT) basis. Descriptive statistics will be used to determine whether there are imbalances at baseline between treatment groups. Baseline variables to be explored are those described in section 7.4.1. Patient-reported outcome scores based on

standardised questionnaires will be calculated based on the developers' scoring manuals and missing and erroneous items will be handled according to these manuals. Continuous measures will be presented as means and standard deviations or medians and ranges depending on their distribution. Categorical data will be presented as frequencies and proportions.

Template tables of baseline data and CONSORT flow charts will be presented in a detailed statistical analysis plan to be approved by the TSC and made publicly available prior to analysis.

11.3.2 Primary outcome analysis

The primary endpoint in this study is quality adjusted life years which will be calculated using EQ-5D-5L data collected 4-monthly and survival data. The primary statistical analyses between the randomised groups will be conducted on an intention-to-treat (ITT) basis. Longitudinal responses to the EQ-5D-5L will be used to generate scores based on the developer's scoring manuals and these will be used to compute QALYs experienced over the follow up period using the area under the curve approach. If the observed QALYs data are normally distributed, the mean differences in QALYs between treatment arms with 95% confidence intervals will be calculated using multivariate linear regression models. Should the data not be normally distributed, however, we will consider the shape of the distribution to inform the choice of alternative, suitable regression models (including non-parametric models) for this outcome.

11.3.3 Secondary outcome analysis

While QALYs helpfully bring together quantity and quality of life in a single score, there will be a number of other experiences and outcomes that are important for the individual patient when they are deciding whether or not to have dialysis. These secondary endpoints – such as overall survival, hospital-free days and a series of patient-reported outcome measures – will capture the factors behind the QALYs and assist in the interpretation of the trial results at all levels, from the policy maker to the individual faced with the choice between dialysis and conservative care.

Survival will be assessed using Kaplan-Meier curves and a Cox proportional hazard model analysis. Hospital-free days will be studied using appropriate regression models - such as the negative binomial model with offset for the duration of follow-up - based on the distribution of the data. Appropriate repeated measures regression models for patient-reported outcome scores will be chosen based on the distribution of each outcome.

11.4 Subgroup analyses

We will conduct pre-planned subgroup analyses to investigate any differential effects according to a number of factors. These will be done by introducing appropriate interaction terms in the regression models. We will carry out these analyses by age at baseline (65-79 years vs 80+ years) and rate of kidney function decline in the 12 months pre-baseline (≤5 ml/min/1.73m^2 vs >5 ml/min/1.73m^2). In the group aged 80+ years we will also stratify according to co-morbidity scores at baseline (<2 vs ≥2) and WHO performance status at baseline (<3 vs ≥3).

11.5 Adjusted analyses and sensitivity analyses

All analyses will be adjusted for age (65-79 yrs vs 80+), rate of decline in eGFR (≤5 vs >5) and site. Furthermore, we will adjust for baseline EQ-5D scores in our analyses of the primary outcome (QALYs). In our analyses of patient-reported outcomes we will also adjust for the value of the outcome at baseline.

Descriptive statistics will be used to identify whether there are imbalances at baseline between treatment groups. Where imbalances are observed, sensitivity analyses will be performed where regression models will be further adjusted for these variables.

Sensitivity analyses will involve studying how many patients in each arm become non-compliant with treatment by either deciding not to start dialysis (participants randomised to prepare for dialysis) or deciding to undergo a dialysis access procedure (participants randomised to prepare for responsive management). We will describe the timing of the move, reason for becoming non-compliant with treatment (where data are available) and the characteristics of patients making this decision.

11.6 Interim analysis and criteria for the premature termination of the trial

A dashboard with red/amber/green thresholds is proposed to help the HTA decide whether the internal pilot should proceed to the full trial. Achieving all green targets would almost certainly mean the pilot proceeding to the full trial, whereas achieving predominantly red targets would almost certainly indicate that a full-scale RCT is not feasible.

% of rate proposed	The number of sites recruiting, based on the target of 16 sites	The recruitment rate per active site month, based on the target of 20% initially increasing to 33% [i]	The % of eligible patients randomised, based on the target of 20% initially increasing to 33% [i]	The % of randomised patients crossing over, based on the estimate of 5% in the power calculation
≥85%	14 sites or more	1.3 pts/mth or more	18% or more	6% or less
60-84%	10-13 sites	0.9-1.2 pts/mth	13-17%	7-9%
<60%	9 sites or fewer	0.8 pts/mth or fewer	12% or less	10% or more

[i] All sites have been allowed a 20% rate of randomisation of eligible patients in months 1-6 of recruitment, increasing to 33% in month 7 with the QRI work. The recruitment rate and % of eligible patients randomised are therefore a combination of (1) 4 sites spending half their pilot time at the lower rate and half their pilot time at the higher rate and (2) 12 sites spending all their pilot time at the lower rate. Pts/mth = participants per active site month.

To further assist with the decision, we will report in all scenarios the numbers of patients at each stage of the flow chart.

At the first DMC meeting, the committee will agree on its charter of operation and advise on the criteria for the need for interim analyses and adoption of formal stopping rules for efficacy or safety. The DMC will be responsible for assessing safety and efficacy; they will be responsible for recommending stopping the trial at any time if there are significant safety or ethical issues. Judgements will be made at their discretion.

Any interim statistical analyses by study arm will be performed by the junior study statistician. They will report unblinded data to the DMC who will discuss the results of the interim analyses with the TSC in a joint meeting if they have concerns about the safety of the RCT. The TSC will then report to the central ethics committee.

A detailed statistical analysis plan will be developed for the approval of the TSC and will be finalised before any interim analyses are undertaken for the DMC.

11.7 Procedure(s) to account for missing data

In order to limit missing patient reported outcome data – including the EQ-5D-5L which informs the primary outcome - if a patient is unable to complete questionnaires due to poor health status these can be completed by a relative or carer. Where this has occurred, it will be documented. Study visits have been designed to impose the least burden on the patient by including home visits and telephone/ video study visits, further maximising follow-up and preventing missing data. We will record whether the patient reported outcome questionnaires are completed by a relative/carer and – where information is available - will record the reasons why visits are not conducted or data not collected.

For long term follow-up of outcomes except quality of life, all participants will be asked on consenting to the RCT to consent to linkage to existing healthcare databases, such as Hospital Episode Statistics, the Office for National Statistics and the UK Renal Registry. This will provide data on commencement of acute or chronic dialysis, hospital admissions for medical and surgical reasons and date and cause of death. This will enable follow up for participants that deviate from the trial protocol or might otherwise be lost to follow-up.

Where missing data exist, sensitivity analyses will be conducted using a range of techniques to impute missing data based on patterns of missingness.

11.8 Economic evaluation

11.8.1 Rationale for inclusion of the economic investigation

Economic evaluation will be undertaken given the potential high economic and quality of life impacts of shifting resources within the area of kidney care in line with the provision of a conservative care pathway. 'Back of the envelope' calculations based on the NHS costs associated with conduct of the trial suggest the importance of conducting a full economic assessment. For the trial, expected costs for both the "prepare for dialysis" and the "prepare for responsive management" interventions were estimated as being approximately £30,000 for "prepare for dialysis" and approximately £3,000 for "prepare for responsive management". The implication is that, on average the delivery of preparing for dialysis will cost approximately £27,000 more per patient over the median of 3 years from entry into the trial (eGFR less than 15 mL/min/1.73m2) to end of follow-up.

This is not, however, sufficient information upon which to base decision-making. These costs include only an NHS perspective and need to be considered with caution given they are based on prices quoted rather than actual costs. Further, costs beyond the health service – personal and social services, third sector costs, informal care costs and other societal costs – are not included in this estimate but are clearly very important in the context of a shift to conservative care where much provision happens outside the formal health sector. It is also difficult at this stage to provide even semi-robust estimates of the relative benefits of preparing for dialysis relative to preparing for conservative care. However, if dialysis produces one additional QALY (through gains in length and/or quality of life) per patient over this period compared to conservative care, then preparing for dialysis would fall within the NICE cost-effectiveness threshold of £20-30k/QALY gained. To avoid reaching the maximum threshold of £30k, the number of QALYs gained would need to be at least 0.9. At values less than this, conservative care would be the more cost-effective option. Note that this 'back of the envelope' analysis assumes that we are only interested in the time horizon of the period of the trial. Given that there is considerable uncertainty about the gains in quality and quantity of life from dialysis in this group, this preliminary estimate suggests that the trial will inform decision-making in this area if an economic evaluation is included. A full economic evaluation is therefore clearly required in the study.

11.8.2 Means of assessment for the economic investigation

The economic evaluation will compare the costs and outcomes of Preparing for Responsive Management with those of Preparing for Dialysis from the perspectives of (a) the NHS and personal social services, and (b) society, from the point of randomisation (i) up to three years based on trial data alone and (ii) to death based on trial data combined with decision modelling. Economic evaluation will take the form of (i) cost-effectiveness analysis using QALYs generated using EQ-5D-5L, (ii) cost-effectiveness analysis using equivalent years of full/sufficient capability gained using ICECAP, (iii) cost consequences analysis using a balance sheet approach including all costs and outcomes presented in disaggregated format.

11.8.3 Data collection

Data will be collected as detailed in section 7.4. Costs from the NHS/personal social services perspective will include costs associated with hospital, hospice and general practice and community care, and will include the costs of facilities, staff salaries and medication. For both interventions, appropriate preparation costs will be included, as will costs associated with delivery of the pathway of care experienced by the patient. Discussion with clinical collaborators prior to the start of the trial will ensure that all relevant resource use is captured. For 'Preparing for responsive management' this pathway is likely to include additional support for the patient and their family/ friend/ carer, as well as routine monitoring. For those 'preparing for dialysis' it will include all visits, scans, surgical appointments and surgical/radiological procedures. Where possible, resource use data will be obtained routinely, through hospital and general practice records, as such data are generally much more complete. Resource use that is not captured through routine sources will be captured through the clinical trial documentation or questionnaires (adapted version of the Client Service Receipt Inventory) administered to patients and their family/ friend/ carer at follow up as appropriate.

11.8.4 Data analysis

Valuations will be assigned to all QALY and capability outcomes based on published UK population tariffs at the end of the study [35, 57]. During the pilot phase, the validity of the ICECAP measures in this population will be assessed, considering construct validity and sensitivity to change. All resource use will be valued using unit costs derived from national sources where these are available, or alternatively through the trial centres. Areas where detailed micro-costing is required (such as in relation to the conservative care package) will be identified early on to enable such micro-costing to take place.

Analysis will be conducted on an ITT basis using an incremental approach. Mean total costs and outcomes will be calculated across all patients and incremental cost-effectiveness ratios for the trial arms will be estimated to produce an incremental cost per QALY gained/cost per year of full capability equivalent gained from both health and societal perspectives. Missing cost and outcome data will be imputed using appropriate methods [58]. To avoid bias, imbalances in baseline utility/capability/costs between the groups will be controlled for [59]. Discounting will be applied at the UK Treasury rate at the end of the study (currently 3.5%). Given the multicentre nature of this study, it may be appropriate to use hierarchical modelling techniques (with explanatory variables stratified into patient and centre levels). It is anticipated that only around one third of patients will have died by the end of the trial and so modelling will be used to extrapolate beyond the trial, to capture costs and impacts for the remaining lifetime. Markov models will be developed to simulate the clinical pathways of patients with end stage renal disease for both economic outcomes; Markov models are appropriate as they can represent situations where patients change from one state to another (for example, the shift to dialysis) as well as experiencing recurrent states (such as remaining on dialysis) over long periods of time. The models will be structured such that clinical pathways are based on the arms of the trial. Transition probabilities, costs and outcome information (in terms of both health-related quality of life, and capability wellbeing) will be taken primarily from the trial, but will be supplemented with information from routine datasets including the UK Renal Registry, as well as published data where necessary; time-dependent probabilities will be used as in other Markov models of ESKD [60]. Time intervals for transitions between states will be based on the four monthly follow-up period within the trial. The effect of uncertainty will be estimated using both deterministic and probabilistic sensitivity analysis. Deterministic sensitivity analysis will focus particularly on those issues where it has been necessary to make assumptions about resource use and/or cost or where particular issues have been encountered (for example, if it appears that economies of scale might result with an overall change in practice but these are not generated with the scale of change within the randomised trial). Probabilistic sensitivity analysis will be used to estimate the joint effect of uncertainty in the model parameters.

Cost-effectiveness acceptability curves will be constructed to show the probability that the results fall below given cost-effectiveness thresholds. They will draw on the joint distribution of incremental costs and effects from the probabilistic sensitivity analysis to summarise uncertainty in the cost-effectiveness estimates. The NICE recommended cost/QALY threshold (currently £20,000 to £30,000/QALY gained [61]) at the time of the completion of the study will be used to judge the cost-effectiveness of the interventions in terms of cost/QALY gained. New research funded through MRC (https://www.mrc.ac.uk/funding/how-we-fund-research/highlightnotices/improving-cross-sector-

comparisons-beyond-qaly/successfully-funded-proposals/) is currently aiming to determine thresholds for the ICECAP measures and these will be applied if there are no NICE recommended thresholds for ICECAP available before the end of the study. Costs broken down by more detailed perspectives (hospital, GPs, social services, third sector, patients, carers and families) will also be presented alongside all primary and secondary outcomes (including the POS-S renal condition specific measure, as well as the generic measures) from the study as a whole, in the form of a cost consequences analysis tabulating the costs and outcomes of the alternative treatment pathways.

12 DATA HANDLING

12.1 Data collection tools and source document identification

All data held in Bristol will conform to the UoB Data Security Policy and in compliance with the General Data Protection Regulation (GDPR) and the Data Protection Act 2018. Data will be entered directly into a case report forms (CRF), patient questionnaires (PQs) and carer questionnaires (CQs). Once completed, and no more than 4 weeks after the study visit, copies of the completed CRFs, PQs and CQs must be sent securely (by post or electronically) to the CTU for entry into the database. Data will be collected on paper*. All data will be entered onto a secure database held on the UoB server, and non-identifiable data will be entered onto a secure web-based database. This will be entered by a member of the Prepare for Kidney Care study team via a secure internet link maintained by UoB Information Services. Data collected on the paper case report forms (CRF) at study centres or as questionnaires from study participants will be identifiable only by participant study number (excluding the 'Personal Contact Details' of the Baseline CRF). Recruitment centres will be responsible for the secure transfer of paperwork by post to the Prepare for Kidney Care study team where it will be stored in a secure locked cabinet in a locked room. Critically, data containing patient identifiable information (e.g. written informed consent forms and Baseline CRF) should be posted via Recorded Delivery (at least) using tamper-proof packaging that is marked 'Private and Confidential', and to the attention of a named trial team member. The Prepare for Kidney Care study team will provide the tamper-proof packaging supplies, and encourage *all* patient data transferred via this secure method.

Trial specific guidelines regarding document transfer will be provided to all centres and should be adhered to. Information capable of identifying individuals and the nature of treatment received will be held in the database with passwords restricted to Prepare for Kidney Care study staff.

**Some participants may request to complete questionnaires online, rather than via paper copies; in such cases these will be completed directly onto a secure web-based database by the participants.*

Standardised tools are being used:

- Co-morbidity: Davies co-morbidity Score [42] & Charlson co-morbidity index [62]
- Physical performance and functioning: WHO performance status [63], Timed "get up and go" [38] & Hand grip strength (Jamar hand dynamometer) [39]
- Quality of life: EQ-5D-5L [33], POS-S renal [34], ICECAP-O[35] /ICECAP-SCM [36], Multimorbidity Treatment Burden Questionnaire [37], PACKS impact on carers questionnaire[40], QUALYCARE post-bereavement survey [41]

A central administrative database will be set up by BTC that prompts the research team when study visits are due and CRFs, PQs and CQs are outstanding.

PIs must keep records of all participating patients (sufficient to link records e.g., CRFs and hospital records), all original signed informed consent forms and copies of the CRF pages.

12.2 Data handling and record keeping

12.2.1 Database Platforms

All administrative and clinical data will be stored in REDCap. REDCap is a secure, web-based electronic data capture (EDC) system designed for the collection of research data. The system has been developed and supported by Vanderbilt University. BTC at the UoB has set up its own infrastructure so that all systems are hosted at UoB.

A Relation Database Management System will be used to provide integration services between administrative and clinical databases. These data will be stored here, to support the workflow of the study team. These data will not be made available for analysis.

12.2.2 Administrative Data

The administrative data will be kept in a secure database that is only accessible from within the UoB firewall. All users will require (at least honorary) contracts with UoB in order to access it.

12.2.3 Clinical Data

The clinical data will be stored on a separate server to administrative data. Anonymised clinical data is linked by a participant ID. Email addresses are collected as they are essential for the correct functioning of the survey feature. The 'Email Address' field is flagged as an identifier and not included in the export for the statistician, so the data set can be considered pseudonymised at export and doesn't need further processing.

12.2.4 System Design

A combination of field type validation, data ranges, logic and thorough testing is used to ensure the quality of the data collected.

12.2.5 Data Entry

Admin Data is entered directly via the website. Clinical data can either be entered in this way or by participants completing online surveys.

12.2.6 Reporting ad Export

Reporting and export procedures for data downloads to common statistical packages (SPSS, SAS, Stat, R) are provided.

12.2.7 Storage

Data are stored in secured UoB servers subject to standard UoB security procedures. The full databases are backed up daily. Additionally, changes are logged every 5 minutes. Disaster/ recovery plans are in place as part of the Service Level Agreement (SLA) we have with IT services.

12.2.8 Security

In order to access the application directly, study team users will be added to the system (following request from the Trial Manager) by the BTC Data Manager.

12.2.9 Auditing

A full audit log catalogues individual changes with date/time, old value, new value and the identity of the user who made the change.

12.3 Access to Data

12.3.1 Source data

The PI will allow monitors from the sponsor (NBT R&I), persons responsible for the audit, representatives of the Research Ethics Committee and of the Regulatory Authorities to have direct access to source data/documents.

12.3.2 Anonymised trial data

The Senior IT Manager (in collaboration with the Chief Investigator) will manage access rights to the data set. Prospective new users must demonstrate compliance with legal, data protection and ethical guidelines before any data are released. We anticipate that anonymised trial data will be shared with other researchers to enable international prospective meta-analyses.

12.4 Archiving

This trial will be sponsored by North Bristol NHS Trust, with UoB as the data custodian. Hard copies of completed case report forms will be kept for 5 years following the end of a study to enable audit of data used in publications. These will be kept at the UoB for this time and then destroyed.

13 MONITORING, AUDIT & INSPECTION

The study will be monitored in accordance with North Bristol NHS Trust's Monitoring SOP. All trial related documents will be made available on request for monitoring and audit by North Bristol NHS Trust, the Research Ethics Committee and available for inspection by other licensed bodies. The monitoring plan will be developed and agreed by the sponsor.

Monitoring and audits undertaken by North Bristol NHS Trust, under their remit as sponsor, or individuals appointed responsibility for monitoring on behalf of the Trust, will ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition). Remote monitoring will be conducted based on information submitted by sites and analysis of the trial database. Site visits will then be initiated using a risk-based approach.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Research Ethics Committee review & reports

Ethical and Health Research Authority (HRA) approval will be sought through the HRA for the trial and the qualitative work embedded within the trial. While the trial raises some ethical issues, we hope the Committee will be reassured by (a) the close involvement of PPI in the development of the

trial and its patient facing information, (b) the requirement for participants to have the mental capacity to voluntarily participate in the trial, (c) the involvement of relatives at the trial information and consent stage, (d) the continuous monitoring of research discussions at the trial information and consent stages, (e) involvement of an expert in Medical Ethics and Law, and (f) the international guidelines-based (3), NICE guidance-consistent (50) conservative care pathway, developed with patient involvement, that will form the intervention.

All research will be performed in accordance with the recommendations guiding biomedical research involving human subjects adopted in the 18th World Medical Assembly, Helsinki, Finland. All staff doing specific research activities will be required to complete training in Good Clinical Practice.

Health Research Authority approval will be sought, where appropriate, for any analyses relating to UK Renal Registry data collected under section 251 of the NHS Act 2006 on nonparticipating patients.

All correspondence with the REC will be retained in the Trial Master File/Investigator Site File. 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 trial is declared ended. The CI will notify the REC of the end of the study and if the study is ended prematurely (including the reasons for the premature termination). Within one year after the end of the study, the CI will submit a final report with the results, including any publications/abstracts, to the REC.

14.2 Peer review

The proposal for this trial has been peer-reviewed through the NIHR HTA peer-review process, which includes independent expert and lay reviewers.

In addition, the protocol has been reviewed by the Trial Management Group and the Sponsor.

14.3 Public and Patient Involvement

Patients and their relatives/carers have been involved in the development of the study design. Their input has led us to focus on quality of life as well as survival, and providing patients and their relatives with clear information to enable informed decisions. It has also emphasised the importance people place on being able to stay at home as much as possible and minimise the impact on family/ friends/ carers. Representatives of the National Kidney Federation have worked with the research team to agree the research topic and randomised-nature of the study. They have attended all three study development meetings.

The topic and trial design have arisen from prior exploratory work with patients. It has been discussed in small focus groups with patients and their families (~10) as well as at a dedicated patient workshop and a local patient association meeting. This has changed the application in three major ways:

- Encouraging us to use a combination of quality and quantity of life as the primary end-point, not just survival.
- Ensuring that a wide range of aspects of quality of life are captured.
- Offering to provide trial information in the patient's home where family members/ friends/ carers can be present and provide support to the patient whilst discussing the details of the trial.

Patients and the public will take an active role in the running of the trial through:

- The Trial Management Group: PPI co-applicants will sit on the TMG.
- The Patient Advisory Group (PAG): This will evolve from the patient workshop held to assess the acceptability of the pathways being tested and the trial design. It will be co-chaired by our PPI co-applicants and provide advice, support and oversight of patients' involvement throughout the study. This group will meet 6 monthly in the first two years then annually.

Members of the PAG will develop patient information and advise on study design to optimise its acceptability to patients. Progress and results from the study will be presented to the group and patient/carer interpretation sought. They will also advise on the best way to disseminate the study findings to patients, including the production of plain English summaries.

Members of the PPI group will be involved in a number of ways – face-to-face meetings, workshops for more in-depth work and email for reviewing documents – in the following activities:

- Optimising the conservative care intervention (months 1-6) to ensure that it is acceptable to patients and carers
- Designing information and consent sheets and advising on the recruitment process
- Reading summaries of the qualitative and QRI findings to ensure that patient concerns are adequately reflected in the analysis
- Developing plain English summaries of the findings that can be used by patients and cares to assist them in making evidence based treatment decisions and developing a dissemination policy.

14.4 Regulatory Compliance

Before any site can enrol patients into the trial, the CI/PI or designee will obtain confirmation of capacity and capability for each site.
For all amendments the CI/PI or designee will confirm with the Sponsor, the HRA (+/- REC) and sites' R&D departments that permissions are ongoing.

14.5 Protocol compliance

There will be no prospective, planned deviations or waivers to the protocol. Accidental protocol deviations can happen at any time, but they must be adequately documented on the relevant forms (see Key Trial Contacts section for link to website) and reported to the CI and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

14.6 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree –

a) the safety or physical or mental integrity of the subjects of the trial; or
b) the scientific value of the trial

The sponsor must be notified immediately of any case where the above definition applies during the trial conduct phase. They will assess the seriousness of any breach as per the appropriate SOP (see Key Trial Contacts section for link to website).

14.7 Data protection and patient confidentiality

The UoB will be the data custodian. All data held in Bristol will conform to the UoB Data Security Policy and in Compliance with the General Data Protection Regulation and Data Protection Act 2018.

Data collected on paper case report forms at study centres or as questionnaires from participants will be identifiable only by participant study number. This will be transported by post or securely electronically to the Prepare for Kidney Care study office at UoB and stored in a secure locked cabinet in a locked room.

Data obtained by paper will also be entered onto and maintained on an SQL Server database system maintained by UoB Information Services. Information capable of identifying individuals and the nature of treatment received will be held in the database with passwords restricted to Prepare for Kidney Care study staff. Information capable of identifying participants will not be removed from UoB or clinical centres or made available in any form to those outside the study.

Patient identification codes will be held by the UoB for 5 years, all other data sources will be stored for 5 years after the close of the study. Personal data (e.g. name and address, or any data from which a participant might be identified) will be withdrawn from the study if this is requested by a participant.

Interviews and appointments will be documented on an encrypted digital recorder which will be locked in a secured cabinet at Population Health Sciences, UoB. Recordings will be transferred onto a computer as soon as possible after each interview and stored only in a password protected drive maintained by the UoB. Only the qualitative researchers working on this study will have access to this drive.

Recordings and transcriptions will be named with a study-assigned participant number, centre initials, and the date of recording. There will be no participant identifiers in files, databases, or transcripts, which will only be labelled with study assigned participant numbers. Coding keys matching the name of the participants with their study participation number will be stored in a password protected spreadsheet, which will be maintained and only accessed by the qualitative researchers. All recordings will be coded and securely transferred to a UoB approved transcription company that has signed the required confidentiality agreements. All transcripts will be anonymised upon receipt.

All electronic data files will (databases and recordings) be saved in a secured computer and to a password protected UoB network space, in accordance with the UoB's data security policies.
All nonessential data will be wiped upon completion of the study. Essential documents will be kept for up to 5 years, after which they will be deleted and all copies destroyed in accordance with the UoB's secure erasure of data policy.

The anonymised interview data (transcripts only) will be uploaded to an 'open data' repository, subject to individual written informed consent from the participants. This will have been fully explained in the Patient Information Sheet and requires participants to initial a specific statement on the Consent Form (if they agree).

14.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The research team and all PIs must disclose any ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial. Competing interests will be reported in all publications and in the final report.

14.9 Indemnity

The necessary trial insurance is provided by the Sponsor. North Bristol NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this trial. The Patient Information Sheet provides a statement regarding indemnity for negligent and non-negligent harm.

14.10 Amendments

The Sponsor will determine whether an amendment is substantial or non-substantial. All amendments will be processed through the HRA and where appropriate the REC. If applicable, other specialist review bodies (e.g. CAG) will be notified about substantial amendments in case the amendment affects their opinion of the study. Amendments will also be notified to NHS R&D departments of participating sites to confirm ongoing capacity and capability to deliver the study.

14.11 Post trial care

Following the end of the trial, continued provision of the conservative care intervention (in the format specified for the trial) will be at the discretion of the normal care team and is likely to depend on the trial results. Participants will be informed of this in the written information given to them when they are considering entering the trial.

14.12 Access to the final trial dataset

Anonymous research data will be stored securely and kept for future analysis. Members of the TMG will develop a data sharing policy consistent with UoB policy. Requests for access to data must be via written confidentiality and data sharing agreements which will be confirmed by the CI (or appointed nominee).

The data sharing agreement will cover limitations of use, transfer to third parties, data storage and acknowledgements. The person applying for use of the data will be scrutinised for appropriate eligibility by members of the research team.

15 DISSEMINATION POLICY

A comprehensive plan for disseminating Prepare for Kidney Care trial results will be developed by TMG which will include PPI co-applicants. The results of the study will be published in academic journals and all participants will be offered a plain English summary of the main findings of the study. Meetings will be arranged with stakeholders to consider the implications of the results and how they will most effectively be translated into clinical practice.

On completion of the trial a final report will be prepared for the Funder (NIHR HTA) and once approved made publicly available on their website. The Funder needs formal notice in advance of all publications and the Funder and Sponsor need to be acknowledged within the publications.

The results of the trial are likely to be highly novel and practice changing and will be targeted at high impact general medical journals such as the BMJ, the Lancet, the New England Journal of Medicine and the Journal of the American Medical Association. Findings will be presented at leading nephrology conferences in Europe (the ERA-EDTA Annual Congress) and North America (The American Society of Nephrology Kidney Week) as well as at the UK Kidney Week, co-hosted by the Renal Association and the multi-disciplinary British Renal Society. Findings will also be used to inform future iterations of the NICE-approved UK Renal Association clinical guidelines and the European Renal Best Practice clinical guidelines on preparing for dialysis.

We will also disseminate the findings through the UK Renal Registry and the UK Renal Association. Both have active twitter accounts with 1.9k and 2.3k followers, respectively. A Prepare for Kidney Care twitter account will be set up to keep interested clinicians, policy makers and patients up-to-date with trial progress. Progress and results will also be reported back to the community through the Renal Association's monthly e-newsletter to all members and through the joint UK Kidney Research Consortium-UK Renal Registry Clinical Study Groups for chronic kidney disease and dialysis. Representatives from the British Kidney Patient Association and National Kidney Federation have worked with us on this bid and they too are active on social media and have established channels for communicating the progress and findings of the study to patients such as regular newsletters, a network of kidney patient associations and annual meetings.

The results of the study will be published in peer-reviewed open access journals and all participants will be offered a plain English summary of the findings.

Once finalised, the protocol will be published in an open access academic journal

15.1 Authorship eligibility guidelines and any intended use of professional writers

The final trial report will be written by the CI with support from the TMG and all co-investigators. All TMG members and co-investigators who have contributed to the design, conduct analysis and write up will be offered authorship on the final report.

On manuscripts arising from the trial, authorship will be on an individual authorship basis (rather than group authorship basis) with inclusion based on the recommendations of the International Committee of Medical Journal Editors.

16 REFERENCES

1. Gilg, J., F.J. Caskey, and D. Fogarty, *UK Renal Registry 18th Annual Report: Chapter 1 UK Renal Replacement Therapy Incidence in 2014: National and Centre-specific Analyses.* Nephron Clin Pract, 2016.
2. Pippias, M., et al., *The changing trends and outcomes in renal replacement therapy: data from the ERA-EDTA Registry.* Nephrol Dial Transplant, 2015. **In press**.
3. Roderick, P., et al., in *A national study of practice patterns in UK renal units in the use of dialysis and conservative kidney management to treat people aged 75 years and over with chronic kidney failure*. 2015: Southampton (UK).
4. Steenkamp, R., A. Rao, and P. Roderick, *UK Renal Registry 17th Annual Report: Chapter 5 Survival and Cause of Death in UK Adult Patients on Renal Replacement Therapy in 2013: National and Centre-specific Analyses.* Nephron, 2015. **129 Suppl 1**: p. 99-129.
5. Kurella Tamura, M., et al., *Functional status of elderly adults before and after initiation of dialysis.* N Engl J Med, 2009. **361**(16): p. 1539-47.
6. Hussain, J.A., A. Mooney, and L. Russon, *Comparison of survival analysis and palliative care involvement in patients aged over 70 years choosing conservative management or renal replacement therapy in advanced chronic kidney disease.* Palliat Med, 2013. **27**(9): p. 829-39.
7. Murtagh, F.E., et al., *Dialysis or not? A comparative survival study of patients over 75 years with chronic kidney disease stage 5.* Nephrol Dial Transplant, 2007. **22**(7): p. 1955-62.
8. Brown, M.A., et al., *CKD in elderly patients managed without dialysis: survival, symptoms, and quality of life.* Clin J Am Soc Nephrol, 2015. **10**(2): p. 260-8.
9. Da Silva-Gane, M., et al., *Quality of life and survival in patients with advanced kidney failure managed conservatively or by dialysis.* Clin J Am Soc Nephrol, 2012. **7**(12): p. 2002-9.
10. De Biase, V., et al., *Prolonged conservative treatment for frail elderly patients with end-stage renal disease: the Verona experience.* Nephrol Dial Transplant, 2008. **23**(4): p. 1313-7.
11. Shum, C.K., et al., *Outcomes in older adults with stage 5 chronic kidney disease: comparison of peritoneal dialysis and conservative management.* J Gerontol A Biol Sci Med Sci, 2014. **69**(3): p. 308-14.
12. Seow, Y.Y., et al., *Trajectory of quality of life for poor prognosis stage 5D chronic kidney disease with and without dialysis.* Am J Nephrol, 2013. **37**(3): p. 231-8.
13. Belasco, A., et al., *Quality of life of family caregivers of elderly patients on hemodialysis and peritoneal dialysis.* Am J Kidney Dis, 2006. **48**(6): p. 955-63.
14. Noble, H., D. Kelly, and D. Hudson, *Experiences of carers supporting dying renal patients managed without dialysis. .* J Adv Nurs, 2013. **69**: p. 1829-1839.
15. Joly, D., et al., *Octogenarians Reaching End-Stage Renal Disease: Cohort Study of Decision-Making and Clinical Outcomes.* J Am Soc Nephrol, 2003. **14**(4): p. 1012-1021.
16. Chan, C.H., et al., *Palliative care for patients with end-stage renal disease: experiences from Hong Kong.* Int J Palliat Nurs, 2007. **13**(7): p. 310-4.
17. Teo, B.W., et al., *Profile of hospitalisation and death in the first year after diagnosis of end-stage renal disease in a multi-ethnic Asian population.* Ann Acad Med Singapore, 2010. **39**(2): p. 79-87.
18. Okamoto, I., et al., *Conservative care for ESRD in the United kingdom: a national survey.* Clin J Am Soc Nephrol, 2015. **10**(1): p. 120-6.
19. Tonkin-Crine, S., et al., *Understanding by older patients of dialysis and conservative management for chronic kidney failure.* Am J Kidney Dis, 2015. **65**(3): p. 443-50.
20. Tonkin-Crine, S., et al., *GPs' views on managing advanced chronic kidney disease in primary care: a qualitative study.* Br J Gen Pract, 2015. **65**(636): p. e469-77.
21. Jager, K.J., et al., *The EQUAL study: a European study in chronic kidney disease stage 4 patients.* Nephrol Dial Transplant, 2012. **27 Suppl 3**: p. iii27-31.

22. Stengel, B., et al., *The French Chronic Kidney Disease-Renal Epidemiology and Information Network (CKD-REIN) cohort study.* Nephrol Dial Transplant, 2014. **29**(8): p. 1500-7.
23. de Goeij, M.C., et al., *Course of symptoms and health-related quality of life during specialized pre-dialysis care.* PLoS One, 2014. **9**(4): p. e93069.
24. Office for National Statistics. *National Population Projections, 2010-Based Projections*. 2011 13th August 2015]; Available from: http://www.ons.gov.uk/ons/rel/npp/national-population-projections/2010-based-projections/rep-2010-based-npp-results-summary.html.
25. Appleby, J., *Spending on health and social care over the next 50 years. Why think long term?* 2013, Kings Fund: London, UK.
26. Department of Health, *National Services Framework - Part 2*. 2005, Department of Health: London, UK.
27. Davison, S.N., et al., *Executive summary of the KDIGO Controversies Conference on Supportive Care in Chronic Kidney Disease: developing a roadmap to improving quality care.* Kidney Int, 2015.
28. Kerr, M., et al., *Estimating the financial cost of chronic kidney disease to the NHS in England.* Nephrol Dial Transplant, 2012. **27 Suppl 3**: p. iii73-80.
29. Carson, R.C., et al., *Is Maximum Conservative Management an Equivalent Treatment Option to Dialysis for Elderly Patients with Significant Comorbid Disease?* Clin J Am Soc Nephrol, 2009. **4**(10): p. 1611-1619.
30. Brown, L., G. Gardner, and A. Bonner, *A comparison of treatment options for management of End Stage Kidney Disease in elderly patients: A systematic review protocol.* The JBI Database of Systematic Reviews and Implementation Reports, 2013. **11**(4): p. 12.
31. Donovan, J.L., et al., *Clear obstacles and hidden challenges: understanding recruiter perspectives in six pragmatic randomised controlled trials.* Trials, 2014. **15**: p. 5.
32. Morton, R.L., et al., *Factors influencing patient choice of dialysis versus conservative care to treat end-stage kidney disease.* CMAJ, 2012. **184**(5): p. E277-83.
33. Oppe, M., et al., *A program of methodological research to arrive at the new international EQ-5D-5L valuation protocol.* Value Health, 2014. **17**(4): p. 445-53.
34. Murphy, E.L., et al., *Understanding symptoms in patients with advanced chronic kidney disease managed without dialysis: use of a short patient-completed assessment tool.* Nephron Clin Pract, 2009. **111**(1): p. c74-80.
35. Coast, J., et al., *Valuing the ICECAP capability index for older people.* Soc Sci Med, 2008. **67**(5): p. 874-82.
36. Sutton, E.J. and J. Coast, *Development of a supportive care measure for economic evaluation of end-of-life care using qualitative methods.* Palliat Med, 2014. **28**(2): p. 151-7.
37. Man, M.S., et al., *Improving the management of multimorbidity in general practice: protocol of a cluster randomised controlled trial (The 3D Study).* BMJ Open, 2016. **6**(4): p. e011261.
38. Podsiadlo, D. and S. Richardson, *The timed "Up & Go": a test of basic functional mobility for frail elderly persons.* J Am Geriatr Soc, 1991. **39**(2): p. 142-8.
39. Roberts, H.C., et al., *A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach.* Age Ageing, 2011. **40**(4): p. 423-9.
40. Noble, H.R., et al., *PAlliative Care in chronic Kidney diSease: the PACKS study--quality of life, decision making, costs and impact on carers in people managed without dialysis.* BMC Nephrol, 2015. **16**: p. 104.
41. Gomes, B., et al., *Variations in the quality and costs of end-of-life care, preferences and palliative outcomes for cancer patients by place of death: the QUALYCARE study.* BMC Cancer, 2010. **10**: p. 400.
42. Davies, S.J., et al., *Quantifying comorbidity in peritoneal dialysis patients and its relationship to other predictors of survival.* Nephrol Dial Transplant, 2002. **17**(6): p. 1085-92.

43. Moher, D., et al., *The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials.* JAMA, 2001. **285**(15): p. 1987-91.
44. Singer, P.A., D.K. Martin, and M. Kelner, *Quality end-of-life care: patients' perspectives.* Jama, 1999. **281**(2): p. 163-8.
45. O'Cathain, A., et al., *Maximising the value of combining qualitative research and randomised controlled trials in health research: the QUAlitative Research in Trials (QUART) study--a mixed methods study.* Health Technol Assess, 2014. **18**(38): p. 1-197, v-vi.
46. group, T.B.s., *Bluebelle study (phase A): a mixed-methods feasibility study to inform an RCT of surgical wound dressing strategies.* BMJ Open, 2016. **6**(9): p. e012635.
47. Donovan, J.L., et al., *Development of a complex intervention improved randomization and informed consent in a randomized controlled trial.* J Clin Epidemiol, 2009. **62**(1): p. 29-36.
48. Donovan, J., et al., *Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. Commentary: presenting unbiased information to patients can be difficult.* BMJ, 2002. **325**(7367): p. 766-70.
49. Wade, J., et al., *It's not just what you say, it's also how you say it: opening the 'black box' of informed consent appointments in randomised controlled trials.* Soc Sci Med, 2009. **68**(11): p. 2018-28.
50. Paramasivan, S., et al., *A simple technique to identify key recruitment issues in randomised controlled trials: Q-QAT - Quanti-Qualitative Appointment Timing.* Trials, 2015. **16**: p. 88.
51. Roderick, P., et al., *An evaluation of the costs, effectiveness and quality of renal replacement therapy provision in renal satellite units in England and Wales*, H.T. Assessment, Editor. 2005: Southampton, UK.
52. Lendrem, D., et al., *Health-related utility values of patients with primary Sjogren's syndrome and its predictors.* Ann Rheum Dis, 2014. **73**(7): p. 1362-8.
53. Conner-Spady, B., et al., *Responsiveness of the EuroQol in breast cancer patients undergoing high dose chemotherapy.* Qual Life Res, 2001. **10**(6): p. 479-86.
54. Jansson, K.A. and F. Granath, *Health-related quality of life (EQ-5D) before and after orthopedic surgery.* Acta Orthop, 2011. **82**(1): p. 82-9.
55. Lillegraven, S., I.S. Kristiansen, and T.K. Kvien, *Comparison of utility measures and their relationship with other health status measures in 1041 patients with rheumatoid arthritis.* Ann Rheum Dis, 2010. **69**(10): p. 1762-7.
56. Kontopantelis, E. *SKBIM: Stata module to generate a sample from a bimodal distribution using normal or skewed (skew-normal) unimodal distributions, as defined by the user*. Statistical Software Components S456917; Available from: http://econpapers.repec.org/software/bocbocode/s456917.htm.
57. van Hout, B., et al., *Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets.* Value Health, 2012. **15**(5): p. 708-15.
58. Faria, R., et al., *A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials.* Pharmacoeconomics, 2014. **32**(12): p. 1157-70.
59. Ridyard, C.H. and D.A. Hughes, *Methods for the collection of resource use data within clinical trials: a systematic review of studies funded by the UK Health Technology Assessment program.* Value Health, 2010. **13**(8): p. 867-72.
60. Howard, K., et al., *The cost-effectiveness of increasing kidney transplantation and home-based dialysis.* Nephrology, 2009. **14**(1): p. 123-132.
61. Appleby, J., N. Devlin, and D. Parkin, *NICE's cost effectiveness threshold.* BMJ, 2007. **335**(7616): p. 358-9.
62. Charlson, M.E., et al., *A new method of classifying prognostic co-morbidity in longitudinal studies: development and validation.* J Chron Dis, 1987. **40**(5): p. 373-383.
63. Oken, M.M., et al., *Toxicity and response criteria of the Eastern Cooperative Oncology Group.* Am J Clin Oncol, 1982. **5**(6): p. 649-55.

17 APPENDICIES

Appendix 1 – Schedule of Procedures for randomised controlled trial

Procedures		**Screening** Face-to-face visits -3, -2, -1 (as required)	**Baseline** Face-to-face visit 1	**Treatment Phase**		**Follow Up** (Linkage)	**Event based**
				Telephone/ video visits 2, 3, 5, 6, 8, 9, 11, 12	Face-to-face visits 4, 7, 10		
Eligibility assessment		√					
Informed consent		√					
Randomisation			√				
Demographics	Age, sex, ethnicity, marital status, education level, distance lived from kidney clinic, alcohol consumption, smoking history		√				
Clinical	Primary renal disease, date first seen by nephrologist, co-morbidities, dietary restrictions, prescribed medication		√				
Resource use	Hospital/nursing home/residential home days/hospice days, other hospital outpatient services, primary care & community services, help from family, friends & carers.		√				
Laboratory tests	Creatinine, urea, albumin, haemoglobin, haematocrit, mean corpuscular volume, sodium, potassium, bicarbonate, corrected calcium, phosphate, intact		√				

	parathyroid hormone, total cholesterol. (From the date of the study visit or the closest date prior to the study visit.)						
Physical assessment	Height, weight, blood pressure, heart rate, waist circumference, timed “get up and go” [38], hand grip strength (Jamar hand dynamometer) [39], WHO performance status. (Details in standard operating procedures.)		√				
Patient reported	EQ-5D-5L [33], POS-S renal [34], ICECAP-O [35]/ICECAP-SCM [36], Multimorbidity Treatment Burden Questionnaire [37]		√				
Family/ friend/ carer reported	PACKS impact on carers questionnaire [40]		√				
Clinical	Co-morbidities, hospital admissions including dates & causes, dialysis access surgery procedures & complications, other surgery, dialysis treatment received, dietary restrictions, prescribed medication, date location & cause of death.			√	√		
Resource use	Hospital/nursing home/residential home days/hospice days, other hospital outpatient services, primary care & community services, help from family, friends & carers			√	√		
Laboratory tests (all done routinely as part of standard care; pre-	Creatinine, urea (pre- and post-dialysis if on haemodialysis), albumin, haemoglobin, haematocrit,			√	√		

dialysis, if on dialysis, unless otherwise stated)	mean corpuscular volume, sodium, potassium, bicarbonate, corrected calcium, phosphate, intact parathyroid hormone, total cholesterol. (From the date of the study visit or the closest date prior to the study visit.)						
Physical assessment	Weight, blood pressure, heart rate, waist circumference, timed “get up and go” [38], hand grip strength (Jamar hand dynamometer) [39], WHO performance status. (Details in standard operating procedures.)				√		
Compliance with trial	Number of home visits by clinical team from renal unit; Number of attendances at CKD clinic; Number of telephone/ video visits from clinical team at renal unit; Number of visits from the palliative care team; Number of telephone/ video visits from the palliative care team; Advance care plan in place produced; Advance care plan reviewed/updated; Cardiopulmonary resuscitation decision documented; Preferred place of death documented			√	√		
Patient reported	EQ-5D-5L [33], POS-S renal [34], ICECAP-O [35]/ICECAP-SCM [36], Multimorbidity Treatment Burden Questionnaire [37]			√	√		

Family/ friend/ carer reported	PACKS impact on carers questionnaire [40], QUALYCARE post-bereavement survey [41]			√	√		
Clinical	Co-morbidities, hospital admissions including dates & causes, dialysis access surgery procedures & complications, other surgery, dialysis treatment received, date location & cause of death.					√	
Resource use	Hospital days, other hospital outpatient services.					√	
Laboratory tests	Creatinine, urea (pre- and post-dialysis if on haemodialysis), albumin, haemoglobin, haematocrit, mean corpuscular volume, sodium, potassium, bicarbonate, corrected calcium, phosphate, intact parathyroid hormone, total cholesterol.					√	
SAE assessments			√	√	√		
SAE reporting							√

Appendix 2 - Registry follow up study

Eligible patients who decline participation in the RCT will be documented in screening logs and invited to consent to participate in a cohort study. The overall aim of this study is to assess the external validity of the randomised controlled trial by comparing three groups of patients:

1. Participants in the Prepare for Kidney Care RCT
2. Non-participants in the Prepare for Kidney Care study RCT who consent for registry follow-up (the focus of this appendix), and
3. People identified from the UKRR as aged 65+ with an eGFR less than 15mL/min/1.73m^2 who were not approached to participate in the RCT. As these patients are not being asked to give individual consent for their data to be analysed, appropriate applications will be made to the Health Research Authority for Section 251 support to carry out this comparison.

More specifically the study will:

- Describe the outcomes of people who were eligible for the Prepare for Kidney Care RCT but chose not to participate (and so received standard care, commencing dialysis or receiving responsive management when indicated)
- Comparing the baseline characteristics of this eligible but not randomised group against patients who participated in the Prepare for Kidney Care RCT and people identified from the UKRR as aged 65+ with an eGFR less than 15mL/min/1.73m^2 who were not approached to participate in the RCT.
- Compare the outcomes of this eligible but not randomised group against patients who participated in the Prepare for Kidney Care RCT and people identified from the UKRR as aged 65+ with an eGFR less than 15mL/min/1.73m^2 who were not approached to participate in the RCT.

Individuals who decline participation in the Prepare for Kidney Care RCT will be provided with written information about the Registry follow-up study. This will be at the end of discussions about participating in the Prepare for Kidney Care RCT and so patients will offered a few days to consider participation in the Registry follow up study. The nurse will:

- Arrange to follow up the decision about participation in the Registry follow up study by telephone/ video or at the next clinic appointment
- Arrange a face-to-face or telephone/ video communication with the patient to obtain informed consent and conduct the baseline interview, physical assessment and administer the questionnaires, probably at the next clinic appointment
- Explain what will happen next in terms of (i) their normal care, (ii) annual questionnaires on patient reported outcomes and (iii) their registry follow up

If, however, they feel ready to decide straight away then progressing to participate in the Registry follow up study on the same day will be permitted.

Data collection for the registry follow up study

Baseline data

Demographic, social, clinical, resource use, laboratory and patient/ carer reported data will be collected by research nurses during study visits at baseline (following consent). The physical assessment will be performed by the research nurse following standard operating procedures. No blood or urine tests are required other than those that will already have been performed as part of routine care.

Table 4 Summary of baseline data for the registry follow up study.

Demographics/ social	Age, sex, ethnicity, marital status, education level, distance lived from kidney clinic, alcohol consumption, smoking history
Clinical	Primary renal disease, date first seen by nephrologist, co-morbidities, dietary restrictions, prescribed medication
Laboratory	Creatinine, urea, albumin, haemoglobin, haematocrit, mean corpuscular volume, sodium, potassium, bicarbonate, corrected calcium, phosphate, intact parathyroid hormone, total cholesterol. (From the date of the study visit or the closest date prior to the study visit.)
Physical assessment	Height, weight, blood pressure, heart rate, WHO performance status. (Details in standard operating procedures.)
Patient reported	EQ-5D-5L [33], POS-S renal [34], ICECAP-O [35]/ ICECAP-SCM [36], Multimorbidity Treatment Burden Questionnaire [37]

Follow up data

There are no study visits following the baseline study visit. All participants will be asked at recruitment to consent to researchers having access to their primary and secondary care clinical notes and to linkage to existing healthcare databases, such as Hospital Episode Statistics, the Office for National Statistics and the UK Renal Registry. This will provide outcomes data such as commencement of acute or chronic dialysis, hospital admissions for medical and surgical reasons and date and cause of death, including for participants that might otherwise be lost to follow up, for example if they move to a non-participating renal unit.

Once a year, participants will be sent a patient questionnaire for completion and return by post. This will continue for the duration of the RCT follow up.

Table 5 Summary of follow up data collection for the registry follow up study

		Annually By post/email
Patient reported	EQ-5D-5L [33], POS-S renal [34], ICECAP-O [35], Multimorbidity Treatment Burden Questionnaire [37]	●
Key: ● Directly reported by participant		

Statistical analyses

We will use descriptive statistics to describe the baseline characteristics of (1) participants in the Prepare for Kidney Care RCT, (2) non-participants in the Prepare for Kidney Care RCT who consent for registry follow-up and (3) people identified from the UKRR aged 65+ with an eGFR less than 15mL/min/1.73m^2 who were not approached to participate in the RCT. This will include age, gender,

social deprivation, rate of decline in eGFR in the past 12 months, co-morbidity and dialysis decision making status. For those patients participating in the RCT and non-participants who consented to registry follow-up, we will also describe differences in quality of life and symptom burden at baseline.

We will use descriptive statistics to describe the outcomes of people eligible for the Prepare for Kidney Care RCT who do consent to registry follow-up as these patients will receive standard care. We will describe the post-baseline rate of decline in eGFR, rate of decline in quality of life, rate of increase in symptoms. We will describe when dialysis is started and – among those who undergo dialysis – survival rates and quality of life on dialysis. Outcomes will also be compared with those of participants in the Prepare for Kidney Care RCT and – where data are available – patients identified from UKRR who are aged 65+ with an eGFR less than 15mL/min/1.73m^2 who were not approached to participate in the RCT.

A full Statistical Analysis Plan will be developed and reviewed by the Trial Steering Committee.

Appendix 3 – Schedule of Procedures for registry follow up study

Procedures	**Screening** Face-to-face visits -3, -2, -1 (as required)	**Baseline** Face-to-face visit 1	**Follow Up** (Linkage and postal)
Eligibility assessment	√		
Informed consent	√		
Demographics		√	
Medical history		√	√
Medications		√	
Laboratory tests		√	√
Height		√	
Weight		√	
Blood pressure		√	
Heart rate		√	
WHO Performance Status		√	
Patient questionnaires		√	√

Appendix 4 – Flow diagram of consent processes

For Health Care Professionals

Information Sheet – so they can decide whether to allow their patients to be assessed.

Health professionals – to allow interviews +/- recording of meetings and discussions re study

- PIS^{hp_quali1}
- CF^{hp_quali1}

For all patients that are eligible

- Invitation letter – to mention audio-recording of research nurse telephone/ video communication
- PIS^{p_info} – to cover providing information about RCT and Registry follow-up and recording discussions
- CF^{p_v} – Verbal consent for audio-recording of research nurse contacts

↓

For patients (^{p}) and carers (^{c}) that agree to Information Contacts

1. Start by getting consent for giving information and the embedded qualitative research:
   - PIS$^{p\&c_info\&quali}$ – to cover giving information about the study and taking part in stage 2 of the qualitative research (patient and carers)
   - CF$^{p_info\&quali}$ – to cover giving information about the study and taking part in stage 2 of the qualitative research (patients)
   - CF$^{c_info\&quali}$ – to cover giving information about the study and taking part in stage 2 of the qualitative research (carers)
2. Then give all eligible participants information about the RCT:
   - PIS^{rct} – to cover RCT, and if they agree to the RCT
3. If they decline the RCT:
   - PIS^{rfu} – to cover Registry follow up

Agree to RCT	Agree to registry follow up only
- CF^{rct} – to cover RCT - CF^{p_quali3} – to cover patient qualitative research phase 3 - Letter to their health professionals In a subset: - PIS^{quali3} – to cover qualitative research phase 3 (patients and carers) - CF^{c_quali3} – to cover carer qualitative research phase 3	- CF^{rfu} – to cover Registry follow up - Letter to their health professionals

Carers (^{C}) – to allow interviews and post-bereavement survey

- PIS^{c_quali3}
- CF^{c_quali3}

Funding Acknowledgement: *This project is funded by the National Institute for Health Research (NIHR) HTA programme (project reference 15/57/39).*

Department of Health Disclaimer: *The views and opinions expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.*

BTC Acknowledgement: *This study was designed and delivered in collaboration with the Bristol Trials Centre (BTC), a UKCRC registered clinical trials unit which, is in receipt of National Institute for Health Research CTU support funding.*

Sponsor: *This study is sponsored by North Bristol NHS Trust.*