Intervening to eliminate the centre-effect variation in home dialysis use

Inter-CEPt

Revisions to protocol Final v1.0 16 July 2020

Changes are effective in protocol Final v2.0 November 2020

Change	Rationale	Affected protocol section
Study start and end dates are added	To confirm the study timeline	10.2 Study timeline

Revisions to protocol Final v2.0 20 November 2020

Changes are effective in Final v3.0 21 June 2021

Change	Rationale	Affected protocol section
Non-participant observation of day to day site activity will be undertaken remotely in instances where relevant meetings or patient education are being delivered virtually. Researchers will join secure remote sessions as observers and participant information and consent processes will follow the protocol for non-participant observation. Researchers can also obtain participant consent by telephone in accordance with study specific telephone guidance. No identifiable patient information will be collected.	To maximise the opportunities for undertaking observations remotely.	7.1 Participant identification, recruitment and consent
Postcodes will only be linked to identifiable patient/carer names after permission from the patient/carer has been given to share these details with the research team. The postcode will be stored securely at the University of Birmingham.	To clarify and confirm that postcodes will be processed in accordance with data protection requirements.	7.1 Patient identification, recruitment and consent

Local site staff will provide one reminder phone call in the event of non-response after 1 week.	Advice from experienced NHS renal nurses is that patients are more likely to recall the study details if the reminder phone call in the event of non-repsone is after 1 week.	7.1 Participant identification, recruitment and consent
For semi-structured qualitative interviews with staff, patients and carers all interviewees will be offered the opportunity to undertake their interview via video-conferencing (MSTeams or Zoom, University of Birmingham enhanced security accounts) if this is preferred to a telephone interview. This may enhance rapport by giving a face-to-face feel to the interviews in instances where in person interviews are restricted. These interviews will follow the same participant information and consent processes as the telephone interviews .	To maximise the opportunities for face to face undertaking of semi-structured interviews remotely.	7.1 Participant identification, recruitment and consent

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

RESEARCH REFERENCE NUMBERS

IRAS Number: 281908

Sponsor Number:RG-0308-20

Funding acknowledgement

This project is funded by the National Institute for Health Research (NIHR) Health Services & Delivery Research (HS&DR) Programme (project reference128364).

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

SIGNATURE PAGE

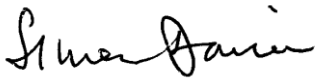
For Keele University sponsored studies, the sponsor will confirm approval of the protocol by signing the IRAS form and therefore a signature on the protocol is not required. The sponsor must be notified of all amendments to the protocol, both substantial and non-substantial. Review of amendments by the sponsor will act as the confirmation that the sponsor confirms approval of the amended protocol.

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, 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 publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature:  Date: 21 June 2021

.....

Name (please print): PROFESSOR SIMON DAVIES

.....

Sponsor statement:

Where Keele University takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

LIST of CONTENTS

LIST OF ABBREVIATIONS

BME	Black and minority ethnicities
CI	Chief Investigator
GCP	Good Clinical Practice
ICF	Informed Consent Form
REC	Research Ethics Committee
SAE	Serious Adverse Event
SMG	Study Management Group
SOC	Study Oversight Committee
SOP	Standard Operating Procedure

Study Specific Treatment Abbreviations and Definitions

HD *Haemodialysis*, a treatment that replaces kidney function by cleaning the blood in a machine with a filter that is external to the body. Typically, this takes 4 hours per treatment, three times a week at reasonably spaced intervals.

CHD *Centre-based haemodialysis,* HD treatment sessions are delivered in the hospital setting (either a unit attached to an in-patient hospital centre, or a stand-alone satellite dialysis unit, away from the main centre). Typically, patients have to fit in with unit schedules and have to travel, in many cases relying on hospital transport.

HHD *Home based haemodialysis* – HD is undertaken by the person with kidney failure at home, often but not always with family support. The timing, duration and frequency of the sessions are more flexible addressing patient preferences or clinical need. In the future assisted HHD (help from a paid non-family member) may become available.

PD *Peritoneal dialysis*, a treatment that replaces kidney function by placing dialysis fluid in the abdominal cavity where it cleans the blood by using the peritoneal membrane (a sack lining the abdominal cavity) as a filter. Typically, this is undertaken at home, occasionally nursing or residential homes, with or without family support. It is continuous but only requires short periods of time to exchange the fluid.

APD *Automated PD*, the dialysis takes place overnight while the patient is asleep but attached to a machine that drains the dialysis fluid in and out, maximising day-time freedom.

aPD *Assisted PD* is when help from a paid non-family member is provided to enable treatment at home for those with barriers to home treatment (difficulty lifting fluid, operating the APD machine).

KEY STUDY CONTACTS

Chief Investigator	Simon Davies Professor of Nephrology and Dialysis Medicine School of Medicine, David Weatherall Building, Keele University, Staffordshire, ST5 5BG s.j.davies@keele.ac.uk 01782 676346 07958133904
Sponsor	Dr Tracy Nevatte Head of Project Assurance, Directorate of Engagement & Partnerships, Innovation Centre 2, Keele University, Staffordshire, ST5 5NH 01782 734714 research.governance@keele.ac.uk
Funder(s)	Health Services and Delivery Research, National Institute for Health Research; NIHR128364
Study Management	Louise Phillips-Darby, School ofMedicine, David Weatherall Building, Keele University, Staffordshire, ST5 5BG l.phillips-darby@keele.ac.uk
Key Protocol Contributors	Professor Lisa Dikomitis, Keele University Dr Mark Lambie, Keele University Dr Ivonne Solis-Trapala, Keele University Mr David Coyle, Devices for Dignity Dr Sarah Damery, Birmingham University Dr Kerry Allen, Birmingham University Dr Iestyn Williams, Birmingham University Dr James Fotheringham, University of Sheffield Dr Harry Hill, University of Sheffield Dr Louise Phillips-Darby, Keele University
Lead Statistician	Dr Ivonne Solis Trapala, Keele University
Committees	Study Oversight Committee (see page 33) This comprises leaders from NHS England, KidneyCare UK, Kidney Research UK, Getting in right first time (GiRFT), National Kidney Foundation (BME representative) and expertise in Applied Health Research, Statistics and Health Economics

STUDY SUMMARY

Study Title	Inter-CEPt: Intervening to eliminate the centre-effect variation in home dialysis use	
Internal Ref. Number (or short title)	Inter-CEPt	
Study Design	A sequential mixed-methods study with the purpose of designing an intervention bundle	
Trial Intervention (where applicable)	Not applicable	
Study Participants	1. Ethnographic study: patients, carers and staff in renal units 2. Survey: Staff or commissioners of care from Dialysis Units in England	
Planned Sample Size	1. Ethnographic study: 6 to 8 short reflection interviews, 10 to12 patients, 5 carers and 12 to 14 staff semi-structured interviews in each of the 4 case study sites. Total 144 (calculated using the average number of interviews per component). 2. Survey: Up to 8 participants across 52 Dialysis Units (likely maximum total: 400)	
Objectives	**Work Package**	**Outcomes**
Gain in-depth insights into cultural and organisational factors contributing to centre variation in uptake	WP1	Insights derived from ethnographic case studies
Understand and quantify the interplay of patient- and centre-level factors, including geography and satellite facilities, affecting uptake, taking into consideration transplantation as a competing treatment and other patient outcomes such as death	WP1,2,3	Quantitative survey, informed by case studies that is linked to patient level Renal Registry data to establish the key factors responsible for centre-level variation which also informs the economic evaluation
Identify factors most likely to be modifiable, effective and easily adopted	WP4	A detailed synthesis of factors that explain centre variation in home therapies uptake
Develop an optimal intervention incorporating these factors that is acceptable to patients and healthcare professionals, taking account of limited financial resources	WP5	Develop candidate components into an intervention bundle derived from the detailed synthesis
Use economic evaluation to develop a contemporary economic model comparing the modalities and establish the cost-effectiveness and return on investment for implementing the intervention bundle	WP3, WP5	Optimised intervention bundle to ensure acceptability, feasibility and cost-effectiveness

Scientific Abstract

RESEARCH QUESTION What are the factors driving centre variation in uptake of home dialysis, and how do these inform the design of an intervention bundle to overcome this?

BACKGROUND Use of home dialysis by centres varies considerably and is decreasing despite attempts to encourage greater use (e.g. NICE guidance). Renal Registry analysis shows underuse of home therapies in ethnic minorities and more socially deprived patients. Health economic analysis suggests more home therapy use would be a potential saving to the NHS but there is significant uncertainty especially when more marginal patients are treated.

AIMS AND OBJECTIVES To gain robust understanding of the factors driving centre variation in the uptake of home dialysis requires an in-depth understanding of the cultural and organisational factors contributing to centre variation and how these relate to quantifiable performance at the local level accounting for competing treatment options. This knowledge will be used to identify which factors would inform a practical and effective intervention bundle embedded within a contemporary economic model of dialysis costs with the objective of ensuring our intervention is realistic and cost effective.

METHODS Underpinned by the NASSS framework our research will use an exploratory sequential mixed methods approach. Qualitative insights derived from multi-sited focused team ethnography, conducted at 4 case-study sites (WP1) will directly inform the intervention as well as the development of a quantitative survey of 52 dialysis centres. A causal graph describing the complex interrelations among patient and centre-level factors leading to uptake of home dialysis and multistate models for the patient treatment and outcome history will be developed (WP2), using the survey results linked to patient level data from the Renal Registry. Economic evaluation (WP3) will also use the Registry data to undertake contemporary cost-effectiveness modelling as well as determining how this might be affected by modification of factors identified in WPs 1&2, so ensuring that the detailed synthesis of factors that explain centre variation in home therapy uptake (WP4) identifies those most likely to yield the greatest cost benefit. This synthesis will lead to selection of candidate components from which we will develop, using the COM-B framework for behaviour change interventions, the optimal intervention bundle (WP5) through workshops with patients and healthcare professionals to ensure acceptability, feasibility and cost effectiveness. PPIE is embedded throughout the project

TIMELINES WP1 informs survey development by 10m and finalises outputs by 18m. WP2 extracts Registry data by 3m, modality use and statistical modelling by 12m, completes survey by 16m finalising linked survey/registry analysis by 22m. WP3 develops contemporary economic model by 15m. Data synthesis (WP4) completes by 24m informs development of intervention bundle by 30m, finalization of outputs 32m.

ANTICIPATED IMPACT AND DISSEMINATION The intervention bundle will comprise components for all stake-holder groups: commissioners, provider units, recipients of dialysis their care-givers and families. Examples include guidance for commissioners, financial incentives, recognition of bias, greater support for certain patient groups, innovative approaches to overcoming barriers. With our advisory group we will ensure that our research reaches all these groups using a variety of methods: events, short guides, infographics, case studies, guidelines, (e.g. NICE, Renal Association), patient conferences, GiRFT initiative, Clinical Reference Group (Dialysis).

Plain English Abstract

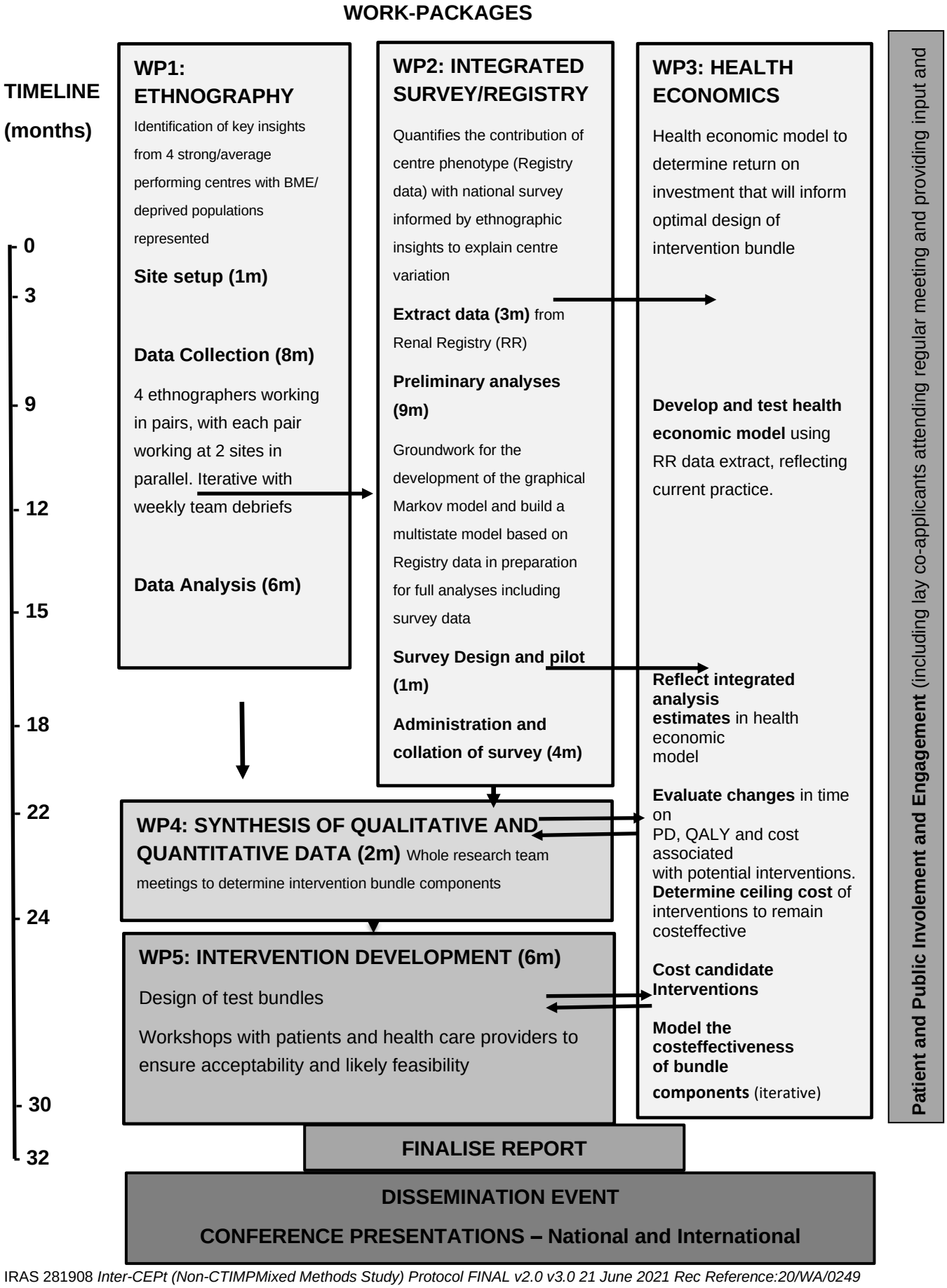
30,000 people with kidney failure in the UK have their treatment, called dialysis, either at home or by travelling to their local dialysis unit as an out-patient, where it is provided by staff. National guidelines encourage the use of home dialysis treatment because there are many advantages. Patients find it more convenient and are more satisfied with their treatment. This greater degree of independence and understanding of their treatment may be why they are more likely to do better on dialysis.

The problem is that some kidney treatment centres provide home treatment to more patients than other centres, varying between 2 and 28% of the total. A recent study from the Renal Registry, a national databank with all the information about kidney patients also found that certain groups in our society were less likely to have home therapy. Those groups include people from black and ethnic minorities and poorer or disadvantaged backgrounds. This is worrying because equality and fairness is important in the NHS. In this study, we aim to understand the complex reasons why home therapies are not used more equally and fairly by kidney centres across the country. We will also design and test a number of possible solutions to improve the uptake of home therapies.

This study has five parts:
(1) Because existing research suggests that the way a centre is organised and how teams work together is important, we will undertake a detailed investigation in four centres with varying success in using home therapies to gain deep insights into the reasons of these differences in uptake. It will involve observing kidney patients, their nurses and doctors, NHS managers, especially how they work together.
(2) We will use these insights to create a survey of all centres across the country. The results will be analysed in a way that incorporates all factors that can explain variation between centre in the use of home therapies, such as the centres' kidney transplant rates, geography and distances for patients to travel.
(3) Because home therapies have been shown to be cheaper, there are potentially very significant savings for the NHS, maybe up to £45 million over 3 years. We will use the information from our research to determine the savings that could be realised.
(4) We will combine all this new knowledge to work out what the most important factors are that are likely to improve home therapy use that is equal and fair.
(5) We will use this research to develop an approach that can be applied by centres that is acceptable to patients and staff as well as being practical and feasible. Examples of what this might include would be illustrations of best practice, how centres use the payments they receive to deliver dialysis care, awareness of prejudice, training in how to avoid this and use of services that assist patients to use home therapies.

This research will benefit patients and the NHS by improving uptake of home therapies, helping people with kidney disease improve their quality of life and reducing costs. Patients will be involved throughout the research in design, interpretation, advising on intervention development, study oversight and reporting, including understandable messages to publicise our findings. We will share the findings with commissioners and service providers through the dialysis Clinical Reference Group and Think Kidneys Home Dialysis campaign as well as more widely to renal and health service conferences and publications.

STUDY FLOW CHART



DETAILED PROJECT DESCRIPTION

1 BACKGROUND

1.1 CURRENT GUIDANCE ON HOME DIALYSIS AND THE EVIDENCE FOR CENTRE VARIATION AND INEQUITY OF ACCESS.

In its most recent critical review (2018), NICE states that dialysis centres should “Offer a choice of dialysis modalities at home or in centre ensuring that the decision is informed by clinical considerations and patient preferences”.[2,3] This is underpinned by evidence of similar survival benefits and equivalent harms when comparing in-centre haemodialysis (CHD) with both peritoneal dialysis (PD, the main type of home therapy) and with home haemodialysis (HHD). It replaces three previous reviews, all of which were supportive of home dialysis treatment.[7-9] Given the very few absolute medical contra-indications to either dialysis modality,[10] choice should primarily reflect patient preference and typical reasons for choosing treatment at home include desire for autonomy, work and leisure activities, family commitments and other life-style factors, balanced against the responsibility associated with home care.[11-13]

Despite this, use of home therapies has declined by 20% between 2011 and 2015. The first in-depth analysis of Renal Registry data[1] found significant variability in the prevalence of home therapies between centres (ranging from 6% to 27% of dialysis patients). This is largely driven by centre variation in the proportions initiating dialysis with PD, 6.3% to 49.7%, or HHD, 0.02% to 6.6%. These disparities are compounded by less home dialysis use in patients from BME and more socially deprived postcodes. 28% of IHD patients are from BME populations, compared to 22% of those using PD and 13% HHD. The proportions treated with PD in centres with high BME populations (>60% of patients on the programme) vary at least two-fold, with a similar discrepancy seen between the least and most deprived quintiles of deprivation across the board.[1] These disparities corroborate earlier research that also indicated that the variation in home dialysis use was largely explained by centre practices, especially reflecting physician preference for home therapies.[14] The Ontario project, developed to increase home therapy use in the Canadian state, identified many sequential barriers to PD with a wide variation between centres in the chances of these being surmounted, even after patients had elected and considered eligible for treatment at home.[15-17] Other explanations include commissioning levers offering financial reward, lack of individualised patient education and emotional support or the use of competing treatments such as transplantation or varied approaches to delivering CHD (such as minimal care facilities or the provision of overnight dialysis shifts).[18,19] These findings point to the culture around home therapies within a centre playing a large part in their uptake and successful use. Maintaining a high prevalent home therapy population also depends on a low technique failure rate. Variation in technique failure is also largely determined by centre characteristics,[20] with better outcomes in centres using home therapies in a higher proportion of patients.[21]

3.2 HEALTH ECONOMIC CONSIDERATIONS.

Kidney replacement treatment (dialysis and transplantation) is needed by 64,000 people in the UK and has a high cost, consuming 1-2% of the NHS budget.[22] The recent NICE review of economic evidence [2,3] was critical of a number of prior reviews and publications that had consistently found home therapies to be more cost effective, raising the concern that they may not be applicable to the UK.[7-9,23,24] Only one Canadian study satisfied the inclusion criteria for their final report, [25] a comparison of PD with HD, estimating a 3-year incremental cost saving per patient of £24,523-45,523 (95%CI) for PD. If this saving could be translated to the UK and the use of PD brought up to the level of the 10 centres that use it most, we estimate this could translate into a 3-year saving to the NHS of between £24 and 45m. Previous publications would have doubled this figure. NICE concluded that the cost of dialysis at home may indeed be lower, but that there was current uncertainty about the differences in costs between PD and CHD due to uncertainty in the methods underpinning current UK dialysis reference costs, and accuracy of transport costs (which are significant, being less for home therapies but not included). They were unable to comment on HHD. There are also other important caveats and gaps in our knowledge. First, this cost saving is not necessarily reflected by the current differential tariffs set for dialysis reimbursement, which are partially designed to reward greater home dialysis use. These tariffs were set when the cost of home therapies was lower and may no longer incentivise home therapy use. While financially incentivising home therapy use does have some positive effects, [18] it is not clear to what extent tariff informs centre variability in dialysis modality use, either because tariff is not a sufficient incentive or because of organisational factors or behaviours operating within the unit. Second, sustainable growth in PD use can be achieved with good outcomes, in particular treatment satisfaction, by expanding its availability to a more elderly comorbid population using an assisted PD program.[26-28] Relative cost-effectiveness of PD in this expanded demographic cannot be assumed. Assisted PD is undertaken to a variable degree in UK centres, attracting a higher tariff, which is potentially offset by the savings on transport costs. However, it is delivered in different ways, e.g. ‘in house’ services versus commercial out-sourcing and thus at variable cost, representing a further significant gap in our knowledge.

2 RATIONALE

2.1 THE PROBLEM

Despite NICE guidance encouraging the use of home dialysis treatment, either by peritoneal dialysis (PD) or home haemodialysis (HHD), its use has fallen over the last few years. Renal Registry analysis indicates that uptake varies considerably by dialysis centre, with significant bias against home dialysis use in people from black and minority ethnicities (BMEs) and less affluent backgrounds.[1]

2.2 WHY THIS RESEARCH IS IMPORTANT

(1) The outcomes for patients who use home dialysis are consistently reported as equivalent or better than those using centre-based dialysis in terms of survival, treatment satisfaction and patient activation - the knowledge, skills and confidence a person has in managing their own health and care.

(2) Access to home therapies should be equitable and not dependent on the enthusiasm of local clinical teams, how dialysis centres organise their services, or patient factors such as ethnicity and socio-economic status
(3) There are good reasons to believe that home therapies are more cost effective than high-cost centre-based dialysis, getting better value for money for the NHS. However, as indicated by the most recent NICE evaluation, there is also significant uncertainty about this. There is an urgent need for more robust and contemporary evidence that takes into account more recent changes in practice, such as assisted home dialysis and the increasing age and prevalence of comorbidity in those requiring dialysis treatment. It has recently been proposed that there will be a national review of dialysis services; our research will inform this process.
(4) A better understanding of the explanations of centre variation in home dialysis use is likely to have generalizable implications, especially for other long-term conditions in which patient participation in management is crucial.

These reasons are closely aligned with the NHS long-term plan which emphasises boosting 'out-of-hospital' care, action on health inequalities, personalised care and maximising the taxpayers' investment, www.longtermplan.nhs.uk

3 AIMS AND OBJECTIVES

1. Gain in-depth insights into cultural and organisational factors contributing to centre variation in uptake.

2. Understand and quantify the interplay of patient- and centre-level factors, including geography and satellite facilities, affecting uptake, taking into consideration transplantation as a competing treatment and other patient outcomes such as death.

3. Identify factors most likely to be modifiable, effective and easily adopted.

4. Develop an optimal intervention incorporating these factors that is acceptable to patients and healthcare professionals, taking account of limited financial resources.

5. Use economic evaluation to develop a contemporary economic model comparing the modalities and establish the cost-effectiveness and return on investment for implementing the intervention bundle

4 STUDY DESIGN AND THEORETICAL/CONCEPTUAL FRAMEWORK

4.1.1 Study Design Overview

This mixed-methods study (see flow chart, page 11) combines qualitative insights derived from ethnographic case studies (**WP1**) with graphical Markov and multistate modelling based on a quantitative survey linked to patient level Renal Registry data (**WP2**) and economic evaluation (**WP3**) to undertake a detailed synthesis of factors that explain centre variation in home therapies uptake (**WP4**). This will inform selection of candidate components from which we will develop the optimal

intervention bundle (**WP5**) through workshops with patients and healthcare professionals to ensure acceptability, feasibility and cost-effectiveness.

The study uses an exploratory sequential mixed-methods design [29]. National data on known variations in uptake of home therapies across England are used to select four case study sites (each case study = one renal unit), where ethnography will be used to explore how and why the centre effect arises and what aspects of renal unit practice affect variation in home therapy uptake amongst black and minority ethnic (BME) and socioeconomically deprived patients in particular. Case studies are a well-established method for studying complex phenomena in their real-life contexts, especially when the boundaries between context and phenomena are not clear [30]. This research is based largely on Stake's approach to case studies, where multiple perspectives are gathered, using a flexible design that allows data collection to adapt in response to experiences in the field, using an inductive approach to analysis [31,32]. The results from this first phase of qualitative data collection will inform a second quantitative phase of research based on graphical Markov modelling that will evaluate the relative contribution of patient and centre-level factors to observed variations in home therapy uptake in both high-performing 'best practice exemplar' case study sites, and in those performing at around the national average for uptake rates. This will allow an assessment of the ways that centre-level and other barriers to home therapy uptake could be overcome via cost-effectiveness modelling of potential interventions.

4.1.2 Theoretical Framework

The theoretical framework for this study is the NASSS framework [4]. Although originally developed in order to explain variation in the adoption of technology in healthcare settings, this framework has wider application arising from its focus on providing explanations for the non-adoption, abandonment or failure to scale-up, spread and sustain innovation in the long-term. The NASSS framework identifies 7 key explanatory factors related to: the condition/illness (in this case end-stage renal disease); the technology (in this case home therapies); the value proposition (to both the patient and the provider); adopters (staff, patients and carers; and their role, identity and input required); organisation (including capacity, capability and readiness to change); the wider system (including policy context, legal issues, socio-cultural context) and embedding and adapting over time. Each factor is considered in relation to complexity theory, prompting an analysis of whether it is simple, complicated or complex [4]. The framework is designed to generate rich descriptions and explanations of the implementation of innovation in real-world settings.

Although home therapies (PD and HHD) have been used to treat end-stage renal disease for many years, uptake rates have remained stubbornly low in England and have failed to be adopted widely despite evidence in favour of positive clinical and patient outcomes and multiple technological developments improving reliability, acceptability and cost within the two home dialysis modalities. The NASSS framework will therefore help to provide a theoretical framework to explain and illuminate how and why some renal units have been able to exceed national average uptake rates.

For the initial stage of intervention development, the study draws on the COM-B framework for designing behaviour change interventions.[5] This framework is now internationally recognised as one of the most robust evidence-based frameworks for behaviour change, and is highly relevant to home therapy uptake, which, as a home-based rather than hospital-based therapy, requires new or different behaviours from patients, carers/family and staff.

5 STUDY SETTING (by Work Package)

5:WP1 Four case study sites selected from the 52 dialysis units in England. Selection of the four case study renal units involved two-stage purposive sampling and was undertaken prior to grant submission. Stage 1 involved assigning each renal unit in England that offers PD and/or home haemodialysis as treatment options for renal patients (n=52) to one of four categories based on a home therapies uptake taxonomy developed using UK Renal Registry data [43]. The four categories in the taxonomy are: i) high uptake of home therapies (top 15% nationally based on the proportion of renal patients at each unit treated using home therapies); ii) high uptake of home therapies amongst BME patients (top 15%); iii) renal units with home therapy uptake for all patients at rates around the national median (ten above the median and ten below); and iv) renal units with home therapy uptake for BME patients at rates around the national median (ten above the median and ten below). As it is important that case study sites have a large enough cohort of patients potentially eligible for participation in the ethnography, renal units with fewer than 50 total renal patients and/or fewer than 20 BME patients were excluded from consideration as part of the Stage 1 sampling process.

Sampling in Stage 1 produced a long-list of potentially eligible renal units within each of the four groups in the taxonomy. Stage 2 involved further sampling to select a single case study site from each group, ensuring a balanced selection based on: maximum geographical variation across England (North, Midlands, South, London); population density of a renal unit's catchment area (urban/rural); sociodemographic characteristics of a unit's patient population (less affluent/affluent/mixed); and ethnic diversity (high/low BME populations). In addition to these criteria, a flexible approach was used in selecting the four case study sites that balanced the need for maximum variation in unit characteristics and practice with practicalities such as sites' willingness to participate in the study and accounting for the potential influence of unit transplantation rate on home therapy uptake. As transplantation may have an impact on home therapy rates, both units that are or are not also transplant centres will be represented.

5:WP2: The survey will be sent to all 52 of the Dialysis Units in England. The survey data will be linked with the patient level routine data returns made from the 52 units to the UK Renal Registry. Linkage will be undertaken at Keele University.

5:WP3: Is all data driven. Research data will be obtained through Keele University and the UK Renal Registry under a data-sharing agreement.

5:WP4: The data synthesis, using aggregated data, will be undertaken by the research team in workshops held on University premises.

5:WP5: The intervention development will be co-designed with an Independent Reference group comprising patients, carers, health professionals and members of the national dialysis reference group. These workshops will be held on University Premises.

In the following sections the protocol is ordered by WORK PACKAGE. Each paragraph is numbered first by the WP indentifier, e.g. WP1: detail on rationale and design where needed, followed by the main section number and the appropriate subsection where relevant in the following order:

6 ELIGIBILITY CRITERIA

7 STUDY PROCEDURES

8 STATISTICS AND DATA ANALYSIS

9 DATA HANDLING

WORK PACKAGE 1 (WP1): QUALITATIVE RESEARCH: A FOCUSSED ETHNOGRAPHY

WP1: RATIONALE

Qualitative research methods, underpinned by an ethnographic approach, are best suited to identify the main factors that facilitate or impede uptake of home therapies and to provide in-depth understanding of the interplay between factors related to health professionals, patients and carers/families, the organisation and its culture [33]. To date, there are limited ethnographic perspectives into the workings of renal units; pioneering research in renal units includes research on chronic kidney disease in paediatric settings [34,35] and on haemodialysis [36,37]. Ethnographic research is conducted in context, and the immersive *in-situ* method allows the research team to gain direct insights into the learning process about choice of treatment place (home or hospital) and treatment type, through contextual observations and interviews [38]. Ethnographic fieldwork will allow the research team to collect several qualitative data sets on different experiences in the round – each representing a particular view based on the position of that stakeholder – and these will then be analysed in accordance with the context in which they were collected [39]. The key stakeholders are those involved in the decision-making process and those who have a stake in home therapies: patients, family and carers and healthcare professionals working in renal units.

WP1: DESIGN

We will use a comparative ethnographic approach – collecting observational, interview and reflective field data across four centres, each centre representing a ‘case study’ considered sufficient to generate new insights [40]. This case study approach will allow the centre effect to be explored by identifying the collective ways, distinct to each unit’s organisational culture, that staff view and undertake their work and how patients respond through their treatment choices. An ethnographic research design is sufficiently unstructured to allow for emergent new findings (e.g. inclusion of new participants whose relevance becomes apparent during the research), but systematic enough to ensure that factors contributing to centre effects in each site can be clearly identified, so that these can be used in later stages of the study [41]. ‘Focussed ethnography’ allows the ethnographers to focus on a particular aspect of a setting (here: everything that relates to home therapy) rather than on the whole socio-cultural system. Ethnographers, working in pairs in each site, will spend nine months

in four case study renal units (see section 5 for detail of case study site selection) researching how choice about treatment is proposed, negotiated and decided.

WP1:6 ELIGIBILITY CRITERIA

Qualitative data will be collected among patients and healthcare professionals in the four renal units. The primary focus will be on patients who will be *starting* renal replacement therapy for the first time, as this is the largest group of patients, and where the range of treatment choices is often greatest. The semi-structured interviews may also include a small number of patients who are already receiving renal replacement therapy, but who need to switch to a new treatment, as discussions about home therapy options are also relevant to this patient group.

Ethnographic data will also be collected from renal unit staff, who will participate in semi-structured interviews to explore in depth how patients are supported to make treatment choices, their reflections on factors that help and hinder treatment choices (particularly for BME and less affluent patients), and what units have done to encourage the uptake of home dialysis amongst these groups of patients.

WP1:6.1 Inclusion criteria (patients)

- Patients expected to start renal replacement therapy with dialysis within the next 3-6 months.
- Patients with unplanned dialysis initiation, even if dialysis has already commenced in whom a decision regarding preferred dialysis modality has not been made
- Patients starting dialysis following a failed kidney transplant.
- Aged 18+
- Carers, family members or individuals supporting eligible patients

WP1:6.1 Inclusion criteria (staff)

- Renal unit staff members who have regular contact with renal patients and who engage in treatment discussions, or who have oversight of decision-making processes within the renal unit (consultants, registrars, specialist home therapy nurses, pre-dialysis nurses, dialysis unit ward staff, dietitians, psychologists/counsellors, clinical lead, business manager)

WP1:6.2 Exclusion criteria (patients)

- Unable to consent to take part, including those with significant cognitive impairment (although mild cognitive impairment will not preclude participation)
- People with acute kidney injury or anticipated to recovery of kidney function

WP1:6.2 Exclusion criteria (staff)

- Renal unit staff with who do not have regular contact with renal patients, who do not engage in treatment discussions, or who do not have oversight of decision-making processes within the renal unit

WP1:7 STUDY PROCEDURES

Data will be collected over a 9 month period in each of the four case study renal units using three qualitative research methods concurrently: non-participant observation; short reflection interviews and

semi-structured individual face-to-face interviews. All of these data collection methods will include renal unit staff and patients, with carers/family members involved in reflection and semi-structured interviews only.

WP1:7.0.1 Access to case study sites and site setup

The four participating centres are:

1. University Hospitals of Derby and Burton NHS Trust
2. Salford Royal NHS Foundation Trust
3. Portsmouth Hospital NHS Trust
4. King's College Hospital, London NHS Foundation Trust

A one-month site set-up period in each participating centre will allow researchers to consult with and engage stakeholders prior to the start of data collection, ensuring all ethical and local approvals are in place [45], and gaining familiarity with the working procedures within each centre. This co-design phase of the ethnographic fieldwork will include conversations with clinical leads, key staff members and patient representatives about how services are organised/experienced and will highlight the areas of the service they see as relevant to the Inter-CEPt study. The team of ethnographers will all have research passports with each site to allow them access to undertake the research.

WP1:7.0.2 Non-participant observation of relevant meetings in each renal unit

The ethnographers will conduct non-participant observation [46-48] of relevant meetings in each renal unit, focussing attention mainly on dialysis choices, how options are discussed and the treatment decision-making processes. These would be 'large' meetings (i.e. not one-to-one patient-healthcare professional consultations). Examples of such meetings include patient education meetings and multi-disciplinary renal team meetings.

Data collection will focus on treatment choice, the information provided around dialysis choice, questions asked and topics discussed during meetings and which assumptions are made, by both patients and health professionals, around dialysis choice and patient characteristics (e.g, BME, socio-economic deprivation, low health literacy). Ethnographic field notes will be written up frequently and discussed weekly with the research team [49,50]. Although most data will be cross-sectional, collected from different patients at single points in time, we will take any opportunities that arise to observe the same patients in different settings/encounters, in order to add depth to their reflections about their treatment decisions.

WP1:7.0.3 Non-participant observation of dialysis choice consultation

The ethnographers will also conduct non-participant observation [46-48] of the consulation in which the healthcare professional discusses dialysis treatment options with the patient. Data collection in this setting will focus on the content of health professional-patient interaction; the information provided to patients on treatment options and how this is relayed; assumptions made by both patients and health

professionals; and the nature of these encounters, including the tone of conversations, language used, verbal and non-verbal reactions.

WP1:7.0.4 Short reflection interviews after individual dialysis choice consultation

Ethnographers will invite patients, and any family members or carers who wish to join, to participate in a short reflection interview (approximately 15 minutes) after the observed dialysis choice consultation. These reflections will take the form of short cognitive interviews [51], incorporating think-aloud techniques. Such reflection interviews will be undertaken with both healthcare professionals (these include renal consultants at renal clearance clinics and specialist pre-dialysis nurses) and patients to investigate both parties' immediate reactions to, and their thoughts and feelings about the appointments. The aim is to generate rich data from small samples, in this case providing evidence about whether home therapy is understood by patients in a consistent way and in the way intended, as well as how well the consultation is meeting its objectives [55].

WP1:7.0.5 Semi-structured interviews

Semi-structured interviews will be undertaken with patients, carers/family members and renal unit staff. Interviews will explore in depth how patients have made their treatment choices and their reflections on factors that have helped or hindered treatment choices, including but not limited to home therapy options. Around half of these interviews will be with BME patients and patients from less affluent/socioeconomically deprived backgrounds. Staff interviews will explore in depth how patients are supported to make treatment choices, their reflections on factors that help and hinder treatment choices – particularly for BME and less affluent patients – and what renal units have done to encourage the uptake of home dialysis amongst these groups of patients. Interviews with patients and staff will take place in a private room in the renal centre or will be conducted via telephone, whichever arrangment is more convenient for each interview participant.

WP1:7.0.6 Secondary data collection

Written documentary data about the field sites will also be collected, such as unit or organisational policies, strategies, notes of meetings and materials produced for patient counselling and education [56].

WP1:7.1 Participant identification, recruitment and consent

Non-participant observation: General observation of: discussions on acute wards about treatment choice; observation in waiting rooms for appointments; open days or group meetings about treatment options and multi-disciplinary team meetings. A formal participant identification and recruitment process will not be undertaken for this strand of data collection, and no identifiable patient information will be collected.

Non-participant observation of one-to-one appointments: Patients and staff members will always be briefed with a participant information sheet and consent form about the presence of the ethnographer

and if they do not wish their one-to-one appointment to be observed (where relevant), they will be able to opt out of this.

Non-participant observation of day to day site activity will be undertaken remotely in instances where relevant meetings or patient education are being delivered virtually. Researchers will join secure remote sessions as observers and participant information and consent processes will follow the protocol for non-participant observation. Researchers can also obtain participant consent by telephone in accordance with study specific telephone guidance. No identifiable patient information will be collected.

Short reflection interviews: These will be think-aloud interviews with nurses and patients (n=6-8 encounters per site; n=24-32 in total). These will be conducted immediately after the healthcare professional appointments. Consent for these reflection interviews will be taken face-to-face from both patient and staff participants straight after each appointment which is the subject of the think-aloud interview. Think-aloud interviews will be audio-recorded using encrypted digital recorders and recordings kept on a secure network drive on University of Birmingham premises before being independently transcribed.

Semi-structured interviews (patients and carers/family members): Semi-structured interviews will be undertaken with 10-12 patients per site (n=40-48 in total), and with 5 carers/family members per site (n=20 in total). Lists of potentially eligible patients will be produced and screened against the inclusion/exclusion criteria by renal unit staff every other month. In order to determine socioeconomic status, home residence postcodes will be converted to a deprivation quartile on the Index of Multiple Deprivation using the online tool Geoconvert (http://geoconvert.mimas.ac.uk).

Postcodes will only be linked to identifiable patient/carer names after permission from the patient/carer has been given to share these details with the research team. The postcode will be stored securely at the University of Birmingham.

Where feasible, a maximum variation sampling frame will be used, to ensure diversity in terms of ethnicity, disadvantage, age, gender and comorbidities, and to include patients who have been through the whole treatment decision-making process as well as those who may only have seen the consultant in a low-clearance clinic.

Patients who match the inclusion criteria will initially be informed about the research by the delegated local site staff, be invited to participate by letter and given a copy of the participant information sheet. Local site staff will provide one reminder phone call in the event of non-response after 1 week.

Patients who have expressed an interest and agreed that their contact details can be shared with the research team will receive a follow up telephone call from a member of the research team to arrange for consent to be obtained and to set up a time and date for the interview.

Patients who wish to participate in a semi-structured interview can be interviewed at the renal unit at their next appointment, with written consent taken at that time by the researcher. Alternatively, interviews can take place by telephone following receipt of a consent form completed and signed by

the participant. Researchers can also obtain participant consent by telephone in accordance with study specific telephone guidance.

For carers/family members, written information about the study and a consent form will be included in the pack sent to the patient, with an invitation to pass these on to their carer or a relevant family member if they would also like to be interviewed.

Interviews will be audio-recorded using an encrypted digital recorder and kept on a secure network drive on University of Birmingham premises before being independently transcribed.

Semi-structured interviews (staff): Semi-structured, interviews will be undertaken with 12-14 staff per site (n=48-56 in total). A staff representative (or R&D staff member) from the local participating site will be delegated the duty of identifying participants and will make the initial approach to these participants, to determine their willingness to be contacted by a member of the study team who will provide further information about the study and undertake consent procedures. A maximum variation sampling frame will be used, to ensure that the perspectives of different staff groups are included. Interviewees will therefore include doctors (consultants, registrars) nurses (specialist home therapy staff, pre-dialysis nurses, ward staff, dialysis units), allied health professionals (dietitian, psychologist/counsellor) clinical lead, and business managers. Interviews will be audio-recorded using an encrypted digital recorder and kept on a secure network drive on University of Birmingham premises, before being independently transcribed.

For semi-structured qualitative interviews with staff, patients and carers all interviewees will be offered the opportunity to undertake their interview via video-conferencing (MSTeams or Zoom, University of Birmingham enhanced security accounts) if this is preferred to a telephone interview. This may enhance rapport by giving a face-to-face feel to the interviews in instances where in person interviews are restricted. These interviews will follow the same participant information and consent processes as the telephone interviews .

WP1:8 QUALITATIVE DATA ANALYSIS

WP1:8.1 Documentary analysis

Analysis of each site's written documents will use conventional content analysis [57] and be undertaken contemporaneously with the ethnographic data collection, so that issues identified from the documentary analysis can be explored further in interviews.

WP1:8.2 Non-participant observations

Data will be collected in the form of field notes of observations. These will be shared via a secure team drive and weekly debriefing meetings will ensure progress, meeting milestones and an iterative data analysis process. No identifiable data will be collected in the observation process.

WP1:8.3 Interviews

Patient, staff and carer/family member interviews, including both the reflection interviews conducted immediately after the consulation and the longer semi-structured interviews, will be transcribed verbatim by a professional transcription company and checked against recordings for accuracy.

WP1:8.3 Data synthesis and analysis

Observational data, ethnographers' field notes and interview transcripts will be imported into the qualitative data-analysis software QSR NVivo 12 for inductive thematic analysis [61]. Each site's data will be analysed separately to capture distinctive centre effects. Two researchers will generate an initial coding framework and fields using a broadly representative sample of 10% of each type of data. Results will be reviewed by the team and adjusted to produce a codebook and coding framework. The analytical approach will be inductive, based on iterative data coding and comparison.

Analysis will be guided by the aim of identifying the specific approaches of units and understanding how different approaches are perceived and acted on by patients. Where data do not fit with existing themes, new themes will be developed or existing ones revised until all the data can be assigned to themes. Data from staff and patients will initially be analysed separately. Data from patients, carers and staff will be combined with the documentary analysis to build up a detailed picture of each site. Themes will then be mapped to the NASSS framework in order to identify the main factors which influence the uptake of home therapies, and how these factors interact. A second stage of analysis will look across the four sites' ethnographies to characterise the centre effect and identify promising practices that can be explored in the subsequent national survey.

WP1:9 DATA HANDLING

The research team will preserve the confidentiality of participants in accordance with the Data Protection Act 1998 and any subsequent data protection laws that supersede it (such as the General Practice Data Protection Regulations (GDPR) 2018). Patients and staff participating in the semi-structured or think-aloud interviews will be assigned a unique identifier (as will carers/family members participating in semi-structured interviews) that links them to the relevant case study site, and all data will be anonymised. All participants will be assured of the confidentiality of the data collected, and will be asked for permission to publish anonymised quotations from their interviews in research outputs.

Field notes and data collected from ethnographic non-participant observation will be kept securely on University of Birmingham premises, on a secure network drive to which only the immediate members of the research team will have access. Interview data will be collected using encrypted recording devices, with audio files securely stored on University of Birmingham network servers. For the purposes of interview transcription, an independent, university-approved transcription company (Clayton Research Support) will be used to which audio files will be securely uploaded. A confidentiality agreement will be signed prior to this work commencing. Interview transcripts will be password protected and also stored on University of Birmingham network servers. Any paper files (such as consent forms) will contain no identifiable data, and will be stored in locked filing cabinets in a

locked office in an area of the Institute of Applied Health Research, University of Birmingham which can be accessed only by swipe card and numerical keycode.

WP1:9.5 Archiving

As per the University of Birmingham's regulations on the retention of research data, anonymised, analysed data will be retained for ten years, and will be securely archived on University of Birmingham premises, with the local PI as data custodian. At the end of the study, with participants' consent, data in the form of anonymised transcribed interviews will be stored in the University of Birmingham Data repository and will be made available to bona fide researchers on request. This process is managed by the University of Birmingham Research Governance Office.

The local participating site is required to archive essential study documents in accordance with local Trust procedures, for 10 years after the 'End of study Declaration' (Date of end of study submission to Regulatory bodies).

WORK PACKAGE 2 (WP2): GRAPHICAL MARKOV AND MULTISTATE MODELLING BASED ON LINKED RENAL UNIT SURVEY AND UK RENAL REGISTRY DATA

WP2: RATIONALE

The findings from WP1 will inform the development of a quantitative national survey of all dialysis units in England (n=52), to identify local patterns of practice, explore explanations behind home therapy uptake rates, and to establish the influence of commissioning strategies. The survey will also include questions that are informed by an up to date rapid literature review. By linking the survey findings to actual outcome data obtained from the renal registry it will be possible to quantify how different factors influence the variation in use of home therapies in the context of competing treatments as well as linking these to clinical outcomes.

WP2: SURVEY DESIGN

Survey design will be based on the literature on known factors influencing home therapy uptake along with the findings from the ethnographic observations and semi-structured patient and practitioner interviews from WP1. WP1 will identify specific approaches of renal units towards supporting patients to make treatment choices, characterise the potentially modifiable components of the centre effect in home therapy uptake, and identify examples of best or promising practice that may work to reduce or eliminate the centre effect. These findings will be used to develop the survey (i.e. qualitative insights converted into semi-quantifiable survey questions), through regular and iterative team meetings, initially within WP1 (up to 9 months) and then for 3 months in WP2.

The survey will take around 20 minutes to complete and will consist – where feasible – of short questions with tick-box style or Likert scale responses, with the option of additional free text responses, in order to maximise response rates and ensure comparability of responses across renal units.

WP2: Survey content

Although the content of the survey cannot be specified in advance of undertaking the ethnographic work, survey questions are likely to cover policy/commissioning issues that may impact on home therapy uptake, issues related to financial considerations, renal unit organisation and practice, the influence of unit leadership, renal unit culture around home therapies, and patient-specific factors. Key lines of enquiry will include but not be limited to:

- The principles underpinning home therapy service provision and whether patients from specific groups are prioritised when offering home treatment options
- What treatment options are provided and the criteria for accessing them
- How renal units respond to diverse population needs or unmet needs, particularly amongst patients from BME and socioeconomically deprived communities
- Factors influencing the pattern of home therapy provision
- Examples of innovative practice, use of new HHD technologies, models of assisted care delivery
- Respondent perceptions about the existence of a home therapies centre effect and the factors associated with it
- When and how patient-practitioner discussions about home therapies occur
- The potential impact of innovations such as incentivisation of home therapies
- The influence of tariff structures on home therapy provision and uptake
- The role of renal unit leadership, hierarchy and management in affecting home therapy uptake

WP2:6 ELIGIBILITY CRITERIA

All renal dialysis units in England (n=52) will be invited to participate in the national survey.

WP2:7 STUDY PROCEDURES

The survey will be created by, and administered using the Online Surveys tool (formerly Bristol Online Surveys), for which University of Birmingham holds an institutional licence. Surveys will be made available to potential participants electronically, via a web link embedded in a brief invitation email. Online Surveys was chosen as the survey platform because it is designed to protect respondent anonymity - the system does not use cookies for survey completion, and information about respondents' IP address cannot be accessed. Survey respondents will be able to take part in the survey in any location, at a time of their choosing, minimising any potential inconvenience of participation in the research. The Online Survey allows participants to save their answers when partway through the survey and return to it later for completion at any point

The survey will be piloted for relevance and readability in the West Midlands with 2-3 renal unit staff who will not be invited subsequently to complete the survey when disseminated, and by the project PPIE representatives.

WP2:7.1 Recruitment

The clinical lead of each dialysis unit across England will be sent a covering email explaining the study and an electronic link to the survey, which will be administered using the secure JISC Online Survey tool (formerly known as Bristol Online Surveys), for which University of Birmingham has an institutional license. Clinical leads will be asked to forward the survey link to key staff within their unit (managers, lead clinicians, nurses, healthcare assistants (HCAs), allied health professionals (AHPs), finance officers), with the aim of obtaining at least 8 responses per renal unit. The survey link will also be sent to commissioners of renal services, who will be identified and approached by the study team member representing NHS England.

The reason for including more than one respondent per centre is to get a range of expertise and thus improved accuracy and completeness of the responses. The questionnaire will be designed such that there will be overlap in the questions answered by team members: for example, the director of the home therapies team will be asked to report on their perception of how financial factors influence clinical practice, while the directorate finance manager will have a more technical understanding of any questions in this domain, but will not be expected to answer clinical questions which are clearly outside their expertise. This will allow us to obtain more detail and test the internal validity of the survey, and where disagreement is identified, to identify potential mechanisms and associated intervention targets for exploration in subsequent work packages.

WP2:7.2 Consent

There will be no formal consent process for the survey – return of the survey will be taken as consent to participate. The front page of the survey will include a tick box for respondents to acknowledge a statement assuring them of the confidential handling of any information they provide in their response. With respect to patient data obtained from the registry, this is not required as the UK Renal Registry has Section 251 approval for research using pseudonymised routinely collected patient data. The agreed process requires an application which is reviewed by the data release group.

WP2:8 STATISTICS AND DATA ANALYSIS

WP2:8.1 Sample size calculation

There is no formal sample size calculation for the national survey as this is not a sample, but a whole country study. The sample size is determined by the number of centres from which we obtain information through the survey, rather than the number of survey respondents per renal unit, which will determine the expertise with which it is completed and thus the accuracy of the information. With approximately 8 responses planned per renal unit, we would expect up to 400 completed surveys to be returned. The total number of patient-level observations is estimated to be around 27,000 and will depend on the number of patients on renal replacement therapy.

WP2:8.2 Planned recruitment strategy

We aim to obtain up to 400 completed surveys over a period of 8 weeks. Several strategies will be used to maximise response rates: endorsement of the survey will be sought via the Renal Association Clinical Directors Forum; reminder emails will be sent to clinical leads by the Birmingham research team 2-3 weeks after initial survey dissemination; up to three follow-up telephone calls will target non-responding or under-represented renal units, and the survey will be publicised via professional networks. Monitoring of the renal unit staff groups returning surveys will be undertaken on an ongoing basis. This will allow us to target under-represented groups with new invitations at the 2-3 week reminder point, as well as reminding non-respondents who have already received the survey to return it. Survey recipients receiving a reminder will have a further 5-6 weeks to respond. Newly-invited survey recipients will receive reminders after 2-3 weeks and will also have an 8-week period during which the survey is open to them. Additionally, although survey responses will be anonymous, respondents will have the option to provide some contact details in order to receive a £25 voucher to reimburse their time spent completing the survey.

WP2:8.3 Statistical analysis plan

Surveys will first be analysed descriptively to map patterns of home therapy service provision across the country, and to identify differences and commonalities in renal unit practice. Respondents' views on service provision, possible improvements and commissioning will also be analysed descriptively, looking for differences and commonalities across stakeholder group (e.g. clinical leads, commissioners) and to provide a preliminary understanding of the relative contribution of different factors (leadership, culture etc.) to the home dialysis centre effect. This analysis will also identify key issues for further exploration in the health economic analysis (WP3). Following linkage of the survey data to the UK Renal Registry patient level data we will undertake the following analyses:

WP2:8.3.1 Summary of baseline data and flow of patients

The individual demographic and clinical characteristics from the linked survey and Renal Registry cohort will be described using frequencies and percentages for categorical data and median and interquantile range for continuous data. A flow chart of patients included in the analysis will also be presented.

WP2:8.3.2 Primary Outcome: graphical Markov modelling of factors that explain the variation in home dialysis uptake

We will employ sequences of regressions [53-64] coupled with a causal graph to define a graphical Markov model that extends path analysis to formulate an explanatory model for home dialysis uptake. The model is formulated by ordering the variables in groups of primary outcomes (e.g. HD uptake), potential intermediary variables (e.g. dialysis unit practices, centre characteristics, policy and commissioning, patient comorbidities) and background variables (Fig 1). The model is developed by fitting ordered sequences of linear or logistic regression models and the strength of associations is

quantified through partial correlation coefficients, with variables located on the left taken as response variables to those located to the right of them in a postulated ordering. The choice and ordering of the variables will be informed by the literature review and the ethnographic study. The associations between two variables in the model can be direct or indirect; for example, a dialysis unit characteristic (e.g. whether it is also a transplant centre) may affect home dialysis use directly or indirectly due to a unit practice identified by the survey. Importantly, it is possible to assess interactions or whether any association holds in the same direction and at the same magnitude for different patient demographics, e.g. ethnicity or socio-economic status.

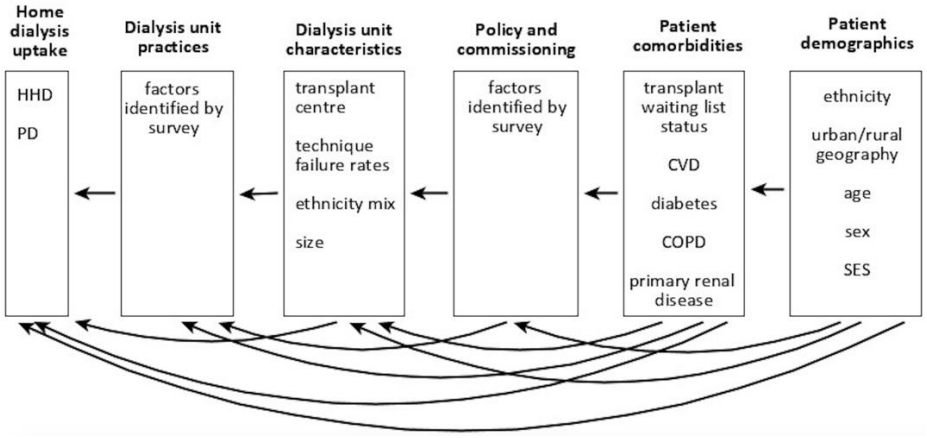


Figure 1: Example of postulated order of sequences of regressions model variables. Variables located on the right are regarded as explanatory to those located to their left. The associations between two variables in different boxes can be direct or indirect through intermediary variables. SES: Socio-economic status

The strength of this approach is that it provides a framework to identify potential causal relationships amongst many patient- and practice-related factors, and their impact on HD uptake, thereby offering a powerful tool to deal with the complexity likely to be identified by the ethnographic study. The main outcomes of this approach include (1) a causal graph that displays pathways of associations starting from demographic factors through intermediary factors, leading to home uptake, indicated by series of variables connected by arrows or lines, including a measure of relative importance – this will help present and greatly simplify the synthesis of findings (WP4); and (2) an interpretation based on graph theory and probabilistic theory to explore the relationship between selected subsets of variables and thus enable the assessment of competing hypotheses. This will provide a robust mechanism for the choice of the most important modifiable and cost-effective factors when developing the intervention (WP5).

WP2:8.3.3 Secondary Outcome Analysis: Multistate modelling of Patient level treatment modality history and mortality

The results from the graphical Markov model will inform the development of a multi-state model,[66] for patients requiring renal replacement therapy. This will estimate the rates of: home and in-centre dialysis uptake, transplantation, transitions from one modality to another, and death (Fig. 2). The model will quantify the impact of changing centre patterns, identified by the graphical Markov model, on the rates of home dialysis usage. The transition rates will include random intercepts at the centre-

level to account for heterogeneity among dialysis units. The estimated parameters of this model will inform the health economic analysis (WP3).

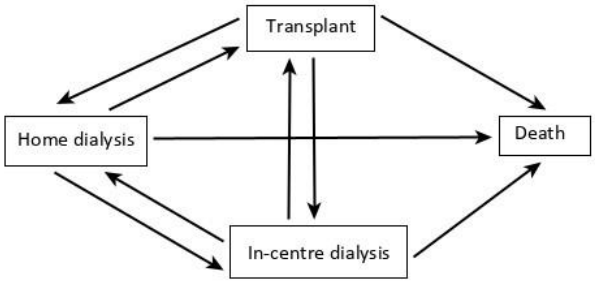


Figure 2. Multi-state model to estimate the rates of home dialysis usage combined, similar models will be built replacing home dialysis by two states for PD and HHD separately allowing transitions between these states

WP2:8.4 Subgroup analyses

There are no a priori planned sub-group analyses. However, it is anticipated that the estimated graphical Markov model in WP2 will be used to assess competing hypotheses during the development of the intervention in WP4.

WP2:8.5 Adjusted analysis

The proposed models will examine the association between any two (or more) variables partitioning out the contribution of different groups of variables as relevant, led by group discussions (WP4). The rates of transitions from the multistate models will be adjusted for age and sex and include important centre-and patient-level explanatory variables.

WP2:8.7 Subject population

All English renal units and all patients commencing renal replacement therapy in them.

WP2:8.8 Procedure(s) to account for missing or spurious data

The survey will be conducted in a manner to minimise the possibility of missing data related to centre practices, with redundancy in the questions posed to different members of the team with different roles in the renal unit. The Renal Registry is characterised by high levels of data completeness, except for comorbidity data as the returns to the Registry from different units are variable. Patterns and levels of missigness will be explored. Maximum likelihood estimation will be used to fit all the models, as this method of estimation yields parameter estimates that are not affected by the exclusion of missing outcome data if a missing-at-random assumption is plausible. Depending on the amount of missing data, expectation-maximisation (EM) imputation will be considered because it preserves the covariance structure of the data, combined with multiple imputation to adjust the estimated standard errors, and thus obtain estimates that make effective use of all the available data.

WP2:9 DATA HANDLING

The Online Survey tool assigns each participant a unique identifying number, and does not record any personal information, cookies, IP addresses or email addresses. Participants will

not be asked to provide any personal information apart from some sociodemographic data (age, gender, ethnic group), and some brief information about their job (role, time in post). This information will be non-identifiable. If any participants disclose personal information via free text survey response options, these will be removed by the research team at the point of exporting survey responses from the Online Survey database to the database that will be kept securely at University of Birmingham for the purposes of analysis.

If respondents have provided any contact details to claim the £25 reimbursement being offered, these details will be removed from the database before analysis.

WP2:9.3 Access to data

Only members of the research team will have access to the anonymised survey data.

WP2:9.4 Data sharing agreements

Keele University will execute the applicable data sharing agreements to enable transfer of study data between collaborating organisations, storage and analysis of data as applicable. These data sharing agreements will include the detail on compliance with the data protection laws as relevant, data controller obligations, data protection particulars with regards to processing and information security arrangements.

WP2:9.5 Survey Data Archiving (before and after linkage to UK Registry Data)

Survey data will be collected in Birmingham and then passed to Keele for linkage to the UK Registry Data. The primary survey data will be archived under the University of Birmingham's regulations on the retention of research data, anonymised, analysed data will be retained for ten years, and will be securely archived on University of Birmingham premises, with the local PI as data custodian.

At Keele University, archiving will be completed as soon as possible after study closure, analysis and dissemination and will be in accordance with Keele University Archiving Standard Operating Procedure. At the end of the study , data will be securely archived in line with the Sponsor's procedures for 10 years after 'End of Study Declaration' (date of end of study submission to Regulatory bodies) and until the sponsor authorises destruction.

WORK PACKAGE 3 (WP3): HEALTH ECONOMICS

WP3:8 ANALYSIS PLAN

The first step in the economic will be to review existing models of UK dialysis services, particularly those submitted for NICE assessment. The purpose of this review will be to inform the conceptualisation of the model including which events to include and the model structure e.g. to use a time to event based model or a state transition model. We will seek feedback on proposed model structures from stakeholders.

After the conceptualisation is near finalised we will undertake a review of parameter values used in existing models to ensure the model is based on the most up to date sources. We will search for estimates of the cost of treatments and the health-related quality of life (HRQoL) associated with dialysis modalities and complications that require hospitalisation. Unit costs will be based on national NHS reference costs and drug prices will be taken from British National Formulary. HRQoL values will be retrieved from the literature or from existing datasets (SHAREHD & UKCath/DOPPS). Regression analysis in UKRR and other data sources for the purpose of quantifying rate of transitions between states or the time until a dialysis event occurs. Minor adjustments to the model structure may take place based on the availability of data in existing datasets.

Once all parameter values have been retrieved we will build the economic model in the software package R. To check the validity of the model we will compare its outputs to those from existing registries and modelling studies and share results at an early stage with stakeholders. Model calibration will take place if there is not a close fit to existing sources, and this would involve adjusting the parameter values of uncertain model inputs to ensure the model outcomes closely reflects findings from registry data. There will be sensitivity testing of parameter inputs to examine which model assumptions and parameter values are the main drivers of the economic outcomes.

WP3:9 DATA HANDLING

WP3:9.1 Data collection tools and source document identification

The UK renal registry data is extracted from the renal computer systems at individual renal centres, and securely transferred to the UK Renal Registry servers in Bristol. The data collection tools (fields, format etc) are defined by the UK Renal Registry dataset and individual centres specific data formats are converted appropriately. There are no standardised data collection instruments at individual sites.

WP3:9.2 Data handling and record keeping

UK Renal Registry data will be imported into the statistical package R, for subsequent reshaping, assessment of missingness, summary statistics and fitting of relevant models which will inform the health economic model. The health economic model will also be run in this environment. WP3 intends to develop analysis scripts that take the raw UK Renal Registy data and produce the relevant results without intermediate files.

WP3:9.3 Access to data

Data will be securely transferred between the UK Renal Registry, Keele and the University of Sheffield. On arrival to the University of Sheffield this anonymised data will be transferred to secure servers with user privilges limiting it’s access to the immediate study team.

WORK PACKAGE 4 (WP4): SYNTHESIS OF QUALITATIVE AND QUANTITATIVE DATA

WP4: Overview

No new data will be collected for WP4. Analysis will combine the data from previous work packages to synthesise and interpret it in order to develop a number of *potential* intervention bundles that could possibly reduce or eliminate the centre effect in home therapy uptake. The impact of these bundles, or bundle components will then, in an iterative process with the data from WP2 and WP3, be assessed using the explanatory statistical model and the updated health economic model in terms of the trade-off between their benefits and ceiling costs.

WP4: Design and theoretical frameworks

Evidence review has highlighted the absence of attempts to integrate data from different components of mixed methods studies [69a]. Our study methods seek to overcome these shortcomings by undertaking a synthesis guided by two complementary frameworks. These frameworks will determine how data from the ethnography, quantitative work and health economics components are described and combined. Most importantly, these frameworks provide a clear structure to guide the synthesis and integration of research findings derived from multiple sources and using multiple methods. First, the factors affecting the uptake of home therapies (WP1 and WP2) will have been mapped onto each domain of the NASSS framework [4] during the course of the study to date (stage 1) (see Table 1).

The evidence for the importance and significance of each factor, its mechanism of action, complexity within each of the seven NASS framework domains and scope for change over time will be discussed in a team workshop (stage 2) which will also look for patterns and themes in the data from different sources. Synthesis will take place iteratively, with opportunities for re-analysis and further exploration of data from WP1-3 following the first team workshop, so that further quantitative analysis of national survey data, qualitative re-analysis of the ethnographic data and generation of associated costs from the health economic model can contribute to the synthesis (stage 3).

After the second round of synthesis, a second team workshop will review the additional analyses and finalise the list of factors affecting home dialysis uptake; identify factors which are co-dependent; use the effect estimates from WP3 to assess the relative impact of each factor on home dialysis uptake, time on home therapy, QALY gains and costs (stage 4). This process will be supported by the review of existing literature which explores the underlying mechanisms. The first intervention development workshop in WP5 will provide an opportunity for the synthesised results to be discussed and challenged by a wider group of staff and patient stakeholders using the APEASE criteria. Alongside the NASSS framework, synthesis will be guided further by the 8-stage process of intervention development outlined by the authors of the COM-B framework.[5] This process will bridge across between WP4 and WP5 so that the intervention development work in WP5 draws on the synthesis undertaken in WP4 and is directly informed by it (see Table 1). The COM-B will also prompt policy-level components of the interventions to be identified.

Table 1: Use of the NASSS framework to guide data synthesis in WP4

Domain	Sub-domain	WP4 Stage 1	WP4 Stage 2	WP4 Stage 3	WP4 Stage 4
Condition (ESRD)	- Nature of condition - Socio-cultural influences	Mapping of findings from WP1 (ethnography), WP2 (quantitative analysis) onto each domain of the NASSS framework to identify potentially modifiable factors affecting home therapy uptake	Research team and stakeholder discussion workshop to refine mapping and identify where further exploration of the data is required. Early identification of mid-range theories	Further quantitative analysis of survey and renal registry data, health economic model and qualitative data from ethnography. Review of literature surrounding early theory within and beyond specific context	Second team workshop to review the additional analyses and supporting evidence, finalise the list of potentially modifiable factors to be taken forward into intervention development work for WP5
Technology (home therapies)	- Features - Knowledge needed to use				
Value proposition (to patient and provider)	- Supply side value (provider) - Demand side value (patient)				
Adopters (roles, identity, input required)	- Staff - Patients - Carers				
Organisational capacity	- Leadership - Readiness to change - Extent of change required - Work needed to implement change				
Wider system (policy)	- Policy context - Regulatory and legal - Professional - Socio-cultural				
Embedding and adapting over time	- Scope - Organisational resilience				
COM-B Stage 1) Define problem in behavioural terms			2) Select the target behaviour to modify		

WORK PACKAGE 5 (WP5): INTERVENTION DEVELOPMENT

WP5: Overview

Consultation with clinical staff and evidence from the literature suggest that a complex intervention will be required (referred to from here as a bundle of interventions), which is comprised of individual elements that act on individual modifiable factors. These modifiable factors are likely to be related to: a) patient-clinician interaction; b) renal unit organisation; and c) the wider policy/system context. In developing the bundle of interventions, we will be guided by the Medical Research Council's internationally recognised principles for developing complex health-related interventions.[6] Broadly, the intervention will be developed and tested with patients and health-care providers to ensure feasibility and acceptability, again working iteratively with the health economics team to ensure cost effectiveness. It is expected that the intervention bundle will comprise a range of components that will have relevance for all stake-holder groups including commissioners, provider units, recipients of dialysis treatment and their care-givers. Potential examples would include commissioning guidance, role and size of financial incentives, recognition of bias, need for greater support for certain groups of patients and caregivers, awareness of opportunities and innovative approaches to overcoming barriers.

WP5:7 STUDY PROCEDURES

Co-design with Reference Group

A co-design approach will be used to develop the intervention over a 6-month period, with patients and clinicians working in an equal partnership with the research team. We will do this by convening an independent Reference Group (RG) of renal clinicians and renal patients that will work with us through three interactive workshops. Membership of the RG will consist of: 4 doctors (consultants, registrars), 4 nurses (home therapy specialist nurses, dialysis nurses, ward nurses), three allied health professionals (dietitian, psychologist/counsellor, social worker); 6 patients (two pre-dialysis, one PD, one home haemodialysis, two in-centre haemodialysis, who will all be members of the national clinical study group for dialysis run by Kidney Research UK); and two policy leads (one national lead, one regional commissioner). Members will be identified through the existing extensive networks of the project team and the advisory group. They will be drawn from across England and will not have had any direct involvement in WP1. The RG will take part in two interactive workshops (one initial full-day workshop, followed by one half-day workshop).

WP5:7.1 Workshop 1

An optional pre-workshop training session or teleconference call will be offered to RG members so that they have an opportunity to understand the design of the study, what data has been collected and what analytical methods have been used. This tailored dialogue should also help to minimise any biases arising from individual members' pre-existing views about home therapies. The first half of Workshop 1 will discuss the synthesised results from WPs 1-3. This will consist of the list of 6-10 modifiable factors that provide the best explanation of centre variation in home dialysis uptake from WPs 1&2, and which will be presented using the six categories of sources of behaviour specified in Michie's COM-B Behaviour Change Wheel.[5] For each of the modifiable factors, we will also present data from WP3 modelling how much each factor could be modified, over what timeframe and to what effect in terms of cost and QALY gains. Following in-depth discussion of the data and opportunities for RG members to challenge or interrogate the data, consensus building techniques will be used to agree a short-list of the 3-5 factors that are most likely to be modifiable *and* likely to have the greatest impact on home dialysis uptake rates.

The second part of Workshop 1 will discuss and identify potential bundles of interventions that could impact upon the short-listed modifiable factors, drawing on the lived experiences of patients and clinicians. The discussion of potential interventions will be structured using the nine intervention categories in the COM-B model, so that the group is encouraged to think about the full range of potential interventions. Members will discuss how proposed interventions might be expected to work and how practical or feasible they might be. The output of the workshop is expected to be 3-5 bundles of interventions that have the potential to eliminate centre variations in home dialysis uptake. Following the workshop, a rapid review of the literature on the 3-5 bundles of interventions will assess evidence for: their feasibility; effectiveness in renal patients and/or patients with other long-term conditions; the feasibility and context in which these interventions have worked previously; and where

possible, information about the active ingredients of success and underlying theories of change. This will be done for individual components of interventions and any bundles of interventions

WP5:7.2 Workshop 2

The second workshop will consider the rapid review evidence and use this to refine the bundles of interventions, paying particular attention to how individual interventions could be packaged together into bundles for maximum impact. The expected output from workshop 2 is 2-3 potential bundles of interventions that will then be modelled for their cost effectiveness to determine the optimal *bundle*, using the health economic model from WP3. The theory of change underpinning each bundle of interventions will also be discussed, in order to identify what the active ingredients are expected to be and how they exert their influence. [6] Table 2 shows how the COM-B framework may inform examples of components to the intervention bundle, which have then been mapped to projected outputs that will, in turn, dictate the appropriate mechanisms of dissemination.

Table 2: COM-B framework domains, potential intervention components

Intervention Categories	**Typical Definitions**	**Examples for this intervention**
Education	Increasing knowledge or understanding	*Raising awareness* of reduced access to home therapies by some groups among clinicians, patients, caregivers and their families
Persuasion	Using communication to induce positive or negative feelings or stimulate action	Comparative publication of the GiRFT performance indicators
Incentivisation	Appropriate commissioning of home dialysis services	Specific guide for commissioners on home dialysis, which might include incentives
Coercion	Creating expectation of punishment or cost	Financial penalties for failing to reach agreed performance indicators
Training	Imparting skills	Unconscious bias training
Restriction	Using rules to increase the target behaviour by reducing the opportunity to engage in competing behaviours	It is likely that specific behaviours that disincentivise home therapies will be identified by the ethnographic study
Environmental restructuring	Changing the physical or social context	*Specific guidance for dialysis providers* how their units are structured to ensure they support home therapy use how finances are managed by service finance departments and unit managers clinic structures, staffing, delivery of assisted dialysis in the home
Modelling	Providing an example for people to aspire to or imitate	*Guidance on Best Clinical Practice*
Enablement	Increasing means/reducing barriers to increase capability or opportunity	Changes to organisational practices that favour culture within a dialysis centre (attitudes, behaviours), for example increasing the time and support for patients, approaches to creating innovative solutions for perceived or actual barriers to home
Policy Categories	**Typical Definitions**	**Examples for this intervention**
Communication/ marketing	Using print, electronic, telephonic or broadcast media	Educational materials, reports, infographics
Guidelines	Creating documents that recommend or mandate practice. This includes all changes to service provision	Next iteration of NICE guidance for the treatment of advanced kidney disease
Fiscal	Using the tax system to reduce or increase the financial cost	In this example, tax = dialysis tariff system. Previous research conducted by this team

		has shown that financial incentives can influence home dialysis use.
Regulation	Establishing rules or principles of behaviour or practice	*Performance Indicators* Indicators for UK Renal Registry Reporting Indicators for the Getting it Right First Time (GiRFT) initiative
Legislation	Making or changing laws	Unlikely to be necessary
Environmental/ social planning	Designing and/or controlling the physical or social environment	Provision of adequate facilities to support home dialysis
Service provision	Delivering a service	Review of service specifications for home dialysis (especially in the context of the planned review of renal services by NHS England)

The remaining sections apply to all 5 study work packages.

10 MONITORING & AUDIT

10.1 Study Management

This is a complex project involving three research departments in different universities with inter-locking work packages running in parallel and tight timelines. These teams have a track record of working together on previous or current research projects, including PDOPPS and the UK-Catheter Study (Keele and Sheffield) [67] and the INTEGRATED project (Keele and Birmingham).[70] The overview of the whole project will be managed from Keele by the CI (Davies), who has extensive experience of running complex projects, supported by an experienced project manager, Louise Phillips-Darby, with an excellent track record in delivering renal research studies. This manager will be responsible for orchestrating the sponsor oversight and requirements of the study (e.g. contracts, IRAS submission, amendments, appointment of Keele researchers as required) and her time is both front- and end-loaded to achieve this (commencing just as soon as the funding is awarded but prior to Time 0 – see plan of investigation above). The PPIE will be managed by Adele Higginbotham (Keele University).

The ethnographic study (WP1), including line-management of the field ethnographers, the national survey (WP2) and the workshops required for the intervention development (WP5) will be managed by the Birmingham team with support of Pamela Nayyar. This team has extensive experience in fieldwork, including within dialysis units in the region, has undertaken many surveys in the past and is experienced in developing quantitative survey questions from qualitative research data. During the ethnographic study there will be frequent team telephone-based feedback discussions (weekly) and monthly face-to-face meetings. To maintain researcher safety when ethnographic data are being collected, the ethnographers will adhere to the University of Birmingham's Code of Practice for the Safety of Social Researchers.

There will be a study management group (Davies, Phillips-Darby, Coyle, Williams, Lambie, Fotheringham, Damery, Allen, Dikomitis) that will have regular monthly meetings or teleconferences

throughout the project, using a standardised agenda, joined on each occasional by the relevant WP lead depending on the immediate requirements for that month. Each WP has defined leadership (see Section 11.0) and will hold its own regular meeting/supervision sessions (at least monthly). The full co-applicant team will meet on at least 2 occasions per year, strategically placed according to the timing of the work-packages. There will be a minimum of two advisory group meetings, (months 6 and 24).

10.1.1 Study Oversight Committee members

The Study Oversight Committee will have representation from the following organisations or expertise

NHS England (Prof Richard Fluck)

Kidney Care UK (Fiona Loud, Policy Director) Chair

Kidney Research Consortium (Elaine Davies, Kidney Research UK)

Patient representative (Fez Awan, BME representative)

Renal Services Transformation Programme (Neil Ashman)

NHS Getting it right first time initiative (Will McCane)

Academic in Health Services Research: Professor Carl Thompson

Academic in Statistics: Professor Peter W. F. Smith

Academic in Health Economics: Professor Pedro Saramago

10.2 Study timeline

Study start date: 01 January 2021
Study end date: 31 August 2023

Month	Key Milestones	Details/Tasks
-6	Notification of award	Initiate preparation of protocol for ethics submission, partnership contracts and research post advertisements where required Finalise arrangements with ethnographic case-study sites, UK Renal Registry and advisory group
-4	Submission of proposal to ethics	
-1	Contracts and sites finalised	
0	Project commences	WPs 1, 2 and 3 commence simultaneously
1 January 2020	Site Setup	WP1 4 sites
4	Data extract from UK Renal Registry	WP2/3 Extract to support model building

6	Advisory group meeting	Share progress and dissemination planning
13	Insights for survey identified	WP2 Use these to design survey and pilot
18	Complete survey	WP2
18	Economic model describing current practice	WP3 reports how cost-effective home-therapies are overall and for specific patient groups
18	Finalise all findings from ethnography	WP1 also prepare for interim presentation and academic publication
23	Complete analysis of linked survey	WPs 2/3 Finalise the statistical analysis and integrate research finding into the economic analysis and prepare interim presentations and academic publications
24	Complete synthesis of qualitative and quantitative data	WP 4
24	Advisory group meeting	Agree overview of intervention
25	PPIE expert group meeting	Inform overview of intervention
31	Finalised intervention bundle	WP5 Following patient/health care provider workshops and further economic modelling of bundle components

11 ETHICAL AND REGULATORY CONSIDERATIONS

11.1 Research Ethics Committee (REC) review & reports

Ethical approval for the whole project was obtained in a single ethics application followed by approval of the study by the Health Research Authority.

The study team will provide regular reports as required to the ethics committee and any study amendments will be approved by the sponsor prior to submission to the ethics committee.

11.2 Peer review

External peer review by the NIHR Health Servcies and Delivery Research Programme.

11.3 Patient and Public Involvement

There will be active PPIE in all aspects of the research. Our patient co-applicants will contribute to the regular investigator meetings held throughout the project (see project management), ensuring the patient perspective is always to the fore. Coyle, who is supported by the NIHR Devices for Dignity MedTech Cooperative where he is employed as their Patient Partnership Lead will, in addition be a member of the Study Management Team, (joining regular meetings by tele-conference) and he will be the patient representative on the ethnography research team. As described in the previous section we

will have two PPIE advisory groups working with us over the duration of the project – an expert group based at Keele, supported by Adele Higginbotham (PPIE Co-ordinator) advising on research design, conduct and dissemination, and a Patient Advisory Group of current or previous users of dialysis treatment who will be supported by Coyle and Davies. This group will be advising on the final stages of the survey development and interpretation, interpretation of ethnographic findings and their dissemination and will contribute to the work shops that are planned for WP5. The latter will be essential in ensuring that the final intervention is grounded by its acceptability and relevance to patients, their care-givers and families. There will also be independent patient representation on the Inter-CEPt Advisory Group drawn from Kidney Care UK. This group will ensure that the project as it develops remains relevant and will provide guidance and networks as needed for dissemination of the projects' outputs.

11.4 Regulatory Compliance

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP) in research studies, and current versions of the UK Policy Framework for Health and Social Care Research. Keele University have a quality management system in place containing standard operating procedures which will be adhered to in the conduct of the study as relevant. Where it is necessary for applicable members of the study team employed by collaborating organisations to adhere to the standard operating procedures executed by their own employer organisation, the delegation of any such responsibilities will be detailed within collaborator agreements. Studies sponsored by Keele University may be subject to an audit by Keele University as the Sponsor for quality assurance.

11.5 Protocol compliance

Deviations from protocols and GCP may occur in research studies. The majority of these instances are technical non-compliances that do not result in harm to the study participants, do not compromise data integrity, or significantly affect the scientific value of the reported results of the study. These technical deviations will be documented, and appropriate corrective and preventative actions will be taken by the research team with responsibility being taken by the CI and where needed with agreement from the Study Oversight Committee.

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

Members of the study team and participating sites are expected to notify Keele University as soon as they become aware of a serious breach. A "serious breach" is a breach which is likely to affect to a significant degree –

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

These will be reported accordingly to Keele University's SOPs.

11.7 Data protection and patient/participant confidentiality

The research team will preserve the confidentiality of participants in accordance with the Data Protection Act 1998 and subsequent data protection laws that supersede it (such as the General Data Protection Regulation – GDPR – 2018), recognising the change in laws around consent. The presentation and reporting of data will remove any information that may lead, directly or deductively, to the identification of individuals.

Confidentiality of qualitative data at research sites and in the transfer of data between research sites and University of Birmingham will be maintained by the ethnographers recording no identifiable data in their field notes (participants will be assigned a unique identifier). Interviews will be recorded using university-approved encrypted digital recorders, and interview transcripts will be anonymised such that any individuals and institutions discussed during interviews cannot be readily identifiable. Participant identifiers will be linked to the participants in a 'code breaker' database which will be password-protected and stored on a password-protected University of Birmingham computer.

Electronic files from the ethnographic research (e.g. interview transcripts, audio-recordings will be held at University of Birmingham on password-protected secure university servers. Only members of the research team will have access. The security of the data stored on the network is governed by the relevant policies of the University of Birmingham (Data Protection Policy, Conditions of Use of Computing and Network Facilities and the University's Research Data Management Policy). Paper copies of research data (e.g. consent forms) will be held securely in a locked archive in a locked office in a swipe-card-restricted area of the University of Birmingham Institute of Applied Health Research.

All surveys in WP2 will be returned directly to University of Birmingham using the secure Online surveys platform, and responses will be downloaded into a database from which any identifying information about individuals will be removed. The survey database will be password-protected and kept securely on University of Birmingham servers, on the network for the Institute of Applied Health Research, to which only the research team will have access. This provides secure, backed up storage of research data, and the folder will be protected by the University's high level of security that protects against spam and virus scanners. In accordance with University of Birmingham's requirements for the storage and retention of research data, study data will be retained for ten years.The only potentially identifiable data that will be retained will be that needed to facilitate linkage with renal registry patient-level data (i.e. job role of survey respondent, and an identifier which can distinguish between renal units). Sharing of data between the UK Renal Registry and the research organisations will be underpinned by data sharing agreements.

The meetings of the Patient Advisory Group and the workshops during WP5 may be audio recorded as deemed necessary by the study team. Consent will be obtained from the meeting participants prior to audio recordings, and relevant working instructions will be followed. Electronic files (containing the researcher's notes of the audio recordings prior to their deletion) will be held securely at the University of Birmingham on password-protected secure servers.

The University of Sheffield complies with the current NHS Digital information governance toolkit (28/03/2019, organisation code 8D715-SHRR). Supplied data is anonymous, and WP3 will go to

additional lengths to prevent patient disclosure such as primary suppression of the reporting of small patient numbers within individual patient sites or with specific conditions or demography.

At Keele University, anonymised study data will be handled and stored in line with Keele University's Data Security Procedures and Standard Operating Procedures, which are in accordance with the Data Protection Act 1998, other relevant regulations such as and GCP guidelines. Keele University's IT organisational security standards follow the requirements of ISO 27001 and follow the UCISA Information Security Toolkit.

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

Simon Davies (CI) receives research funding from and is on an Advisory Board for Baxter Healthcare and research funding from Fresenius Medical Care (both companies that deliver dialysis treatments including home dialysis). Mark Lambie receives research funding from Baxter Healthcare. James Fotheringham has received speaker honoraria from Fresenius medical care, consultancy fees from Novartis, travel support from Amgen, and conducts research funded by the National Institute of Health Research and the Health Foundation into in-center haemodialysis, Kidney Research UK into peritoneal dialysis, and Vifor Pharma into pharmacotherapies for unaemic pruritis.

11.9 Indemnity

The study is sponsored by Keele University and therefore Keele University will be liable for negligent harm caused by the design of the study.

The NHS has a duty of care to patients treated, whether or not the patient is taking part in a study, and the NHS organisation remains liable for clinical negligence and other negligent harm to patients under this duty of care.

Agreements between the sponsor and participating NHS organisations detailing study conduct and the responsibilities to be honoured by each party will be fully executed before the study can start at the local NHS Trust.

11.12 Access to the final trial dataset

At the end of the study, with participants' consent, data in the form of anonymised transcribed interviews will be stored in the University of Birmingham Data repository and will be made available to bona fide researchers on request.

Keele University is committed to sharing access to the study anonymised survey data. Requests for access to the anonymised data from anyone outside of the study team (eg. Collaboration, joint publication, data sharing requests from publishers) will be reviewed. On this basis, these anonymised data will be kept electronically and may be used in other research studies.

12 DISSEMINATION POLICY

12.1 Dissemination policy

Presentations of research will be made on an on-going basis during and after the project to national meetings of relevant stakeholders; e.g. interdisciplinary conferences of the British Renal Society/Renal Association, National Kidney Federation Patient conference, Health Services Research conference; the Clinical Reference Group (CRG); the GiRFT team; regional commissioners. These will include:

Interim Results at appropriate time points: (a) findings of the ethnographic study (after month 18); (b) findings of the National Survey (after month 22); (c) findings of the statistical and health economic modelling (after month 28); (d) the finalised intervention (Study end).

A project report will be produced for the NIHR from which executive summaries will be created that are targeted at specific stake-holders, e.g. guidance and take home messages for commissioners, clinicians, providers, patients and caregivers, each supported by easily digestible *infographics* and *example case studies* produced with the support of our PPIE groups, using plain English, that illustrate the key learnings from the research. These will be disseminated widely via the networks represented on our Advisory Group. Key findings will be disseminated via social media platforms used by dialysis patients (e.g. Facebook networks) and clinicians (Twitter feed).

Academic articles We anticipate a minimum of four open access peer-reviewed academic publications to include research findings of (a) ethnography, (b) graphical Markov modelling, multi-state model, (c) health economic modelling and (d) description of how the final intervention bundle was derived.

Clinical Guidelines We will work with the Renal Association Clinical Guidelines Group to ensure that these are informed by our research and we will seek representation from the Inter-CEPt group on the next iteration of NICE guidelines.

13 REFERENCES

1. Tabinor M, Casula A, Wilkie M, Davies S, Caskey F, Lambie M. UK Renal Registry 19th Annual Report: Chapter 13 Home Therapies in 2015: National and Centre-specific Analyses. *Nephron*. 2017;137 Suppl 1:297-326
2. NICE Renal replacement therapy and conservative management. *NICE Guidline* 107, 2018 nice.org.uk/guidance/ng107
3. NICE Renal replacement therapy and conservative management. Modalities of Renal Replacement Therapy, Evidence Review *NICE Guideline* 107, 2018 nice.org.uk/guidance/ng107
4. Greenhalgh T, Wherton J, Papoutsi C, et al. Beyond Adoption: A New Framework for Theorizing and Evaluating Non-adoption, Abandonment, and Challenges to the Scale-Up, Spread, and Sustainability of Health and Care Technologies. *J Med Internet Res*. 2017 Nov 1;19(11):e367
5. Michie S, van Stralen, MM, West R. The behaviour change wheel: A new method for characterising and designing behaviour change interventions. *Implementation Science* 2011; 6: 42.
5a. Flodgren G, Eccles MP, Shepperd S, Scott A, Parmelli E, Beyer FR. An overview of reviews evaluating the effectiveness of financial incentives in changing healthcare professional behaviours and patient outcomes. Cochrane Database Syst Rev. 2011 Jul 6;(7):CD009255
6. Craig P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions. Prepared on behalf of the Medical Research Council, London, United Kingdom, 2019

7. NICE Renal Replacement Services for adults, *Quality Standard* 72, 2014 nice.org.uk/guidance.nice.org.uk/qs72
8. NICE Home Haemodialysis *Technology Assessment* 48, 2002 nice.org.uk/guidance.nice.org.uk/ta48
9. NICE Peritoneal Dialysis Clinical Guideline 125, 2011 nice.org.uk/guidance.nice.org.uk/cg125
10. Chan CT, Blankestijn PJ, Dember LM, Gallieni M, Harris DCH, Lok CE, Mehrotra R, Stevens PE, Wang AY, Cheung M, Wheeler DC, Winkelmayer WC, Pollock CA; Conference Participants. Dialysis initiation, modality choice, access, and prescription: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2019 Jul;96(1):37-47
11. Ladin K, Lin N, Hahn E, Zhang G, Koch-Weser S, Weiner DE. Engagement in decision-making and patient satisfaction: a qualitative study of older patients' perceptions of dialysis initiation and modality decisions. *Nephrol Dial Transplant*. 2017 Aug 1;32(8):1394-1401.
12. Cassidy BP, Harwood L, Getchell LE, Smith M, Sibbald SL, Moist LM. Educational Support Around Dialysis Modality Decision Making in Patients With Chronic Kidney Disease: Qualitative Study. *Can J Kidney Health Dis*. 2018;8;5:2054358118803323.
13. Tong A, Palmer S, Manns B, Craig JC, Ruospo M, Gargano L, Johnson DW, Hegbrant J, Olsson M, Fishbane S, Strippoli GF. The beliefs and expectations of patients and caregivers about home haemodialysis: an interview study. *BMJ Open*. 2013 24;3(1).
14. Castledine C, Gilg J, Rogers C, Ben-Shlomo Y, Caskey F. UK Renal Registry 13th Annual Report Chapter 15: UK renal centre survey results 2010: RRT incidence and use of home dialysis modalities. *Nephron Clin Pract*. 2011;119 Suppl 2:c255-67
14a. Jayanti A, Foden P, Rae A, et al. The influence of Renal Centre and Patient Sociodemographic Factors on Home Haemodialysis Prevalence in the UK. 2017; 136 (2): 62-74
15. Oliver MJ, Garg AX, Blake PG, Johnson JF, Verrelli M, Zacharias JM, Pandeya S, Quinn RR. Impact of contraindications, barriers to self-care and support on incident peritoneal dialysis utilization. *Nephrol Dial Transplant*. 2010 Aug;25(8):2737-44
16. Prakash S, Perzynski AT, Austin PC, Wu CF, Lawless ME, Paterson JM, Quinn RR, Sehgal AR, Oliver MJ. Neighborhood socioeconomic status and barriers to peritoneal dialysis: a mixed methods study. *Clin J Am Soc Nephrol*. 2013;8(10):1741-9
17. Mann BS, Manns BJ, Barnieh L, Oliver MJ, Devoe D, Lorenzetti D, Pauly R, Quinn RR. Peritoneal Dialysis: A Scoping Review of Strategies to Maximize PD Utilization. Perit Dial Int. 2017;37(2):159-164
18. Combes G, Allen K, Sein K, Girling A, Lilford R. Taking hospital treatments home: a mixed methods case study looking at the barriers and success factors for home dialysis treatment and the influence of a target on uptake rates. *Implement Sci*. 2015;27;10:148
19. Combes G, Sein K, Allen K. How does pre-dialysis education need to change? Findings from a qualitative study with staff and patients. *BMC Nephrol*. 2017;23;18(1):334
20. Htay H, Cho Y, Pascoe EM, et al. Multicenter Registry Analysis of Center Characteristics Associated with Technique Failure in Patients on Incident Peritoneal Dialysis. *Clin J Am Soc Nephrol*. 2017 Jul 7;12(7):1090-1099
21. Pieper D, Mathes T, Marshall MR. A systematic review of the impact of center volume in dialysis. *BMC Res Notes* 2015;22;8:812
22. Kerr M, Bray B, Medcalf J, O'Donoghue DJ, Matthews B. Estimating the financial cost of chronic kidney disease to the NHS in England. *Nephrol Dial Transplant*. 2012;27 Suppl 3:iii73-80
23. Treharne C, Liu FX, Arici M, Crowe L, Farooqui U. Peritoneal dialysis and in-centre haemodialysis: a cost-utility analysis from a UK payer perspective. Appl Health Econ Health Policy. 2014 Aug;12(4):409-20
24. Pike E, Hamidi V, Ringerike T, Wisloff T, Klemp M. More Use of Peritoneal Dialysis Gives Significant Savings: A Systematic Review and Health Economic Decision Model *J Clin Med Res*. 2017;9(2):104-116

25. Chui BK, Manns B, Pannu N, Dong J, Wiebe N, Jindal K et al. Health care costs of peritoneal dialysis technique failure and dialysis modality switching. *American Journal of Kidney Diseases*. 2013; 61(1):104-11
26. Iyasere OU, Brown EA, Johansson L, et al Quality of Life and Physical Function in Older Patients on Dialysis: A Comparison of Assisted Peritoneal Dialysis with Hemodialysis. *Clin J Am Soc Nephrol*. 2016;11(3):423-30
27. Iyasere O, Brown E, Gordon F, Collinson H, Fielding R, Fluck R, Johansson L, Morgan N, Stoves J, Vardhan A, Woodrow G, Davenport A. Longitudinal Trends in Quality of Life and Physical Function in Frail Older Dialysis Patients: A Comparison of Assisted Peritoneal Dialysis and In-Center Hemodialysis. *Perit Dial Int.* 2019;39(2):112-118.
28. Boyer A, Solis-Trapala I, Tabinor M, Davies SJ, Lambie M.Impact of the implementation of an assisted peritoneal dialysis service on peritoneal dialysis initiation Nephrol Dial Transplant, 2019 final stages of acceptance
29. Creswell, J.W. and Plano-Clark, V.L. Designing and Conducting Mixed Methods Research 2011, 2nd edition, SAGE Publications, California, USA.
30. Yin, R. Case study research and applications. 2018, 6th edition. SAGE Publications, California, USA.
31. Yazan B. Three Approaches to Case Study Methods in Education: Yin, Merriam, and Stake *The Qualitative Report*, 2015:20 (2), pp. 134-152.
32. Stake, R. E. Qualitative Case Studies. In: Denzin N.K and Lincoln Y.S (Eds.), The Sage handbook of qualitative research. SAGE Publications, California, USA. 2005 pp. 443-466.
33. Leslie, M., Paradis, E., Gropper, M.A., Reeves, S. and Kitto, S. Applying ethnography to the study of context in healthcare quality and safety. BMJ Qual Saf, 2014:23(2):99-105
34. Lindsay Waters, A. An ethnography of a children's renal unit: experiences of children and young people with long-term renal illness. *Journal of Clinical Nursing*, 2008;17(23); 3103-3114
35. Nightingale, R., Sinha, M.D. and Swallow, V.,. Using focused ethnography in paediatric settings to explore professionals' and parents' attitudes towards expertise in managing chronic kidney disease stage 3–5. *BMC Health Services Research*, 2014;14(1), p.403
36. Aswanden, C.,. Discovering the culture of haemodialysis units: An ethnography. *EDTNA-ERCA Journal*, 2003;29(4), pp.192-194.
37. Blogg, A. and Hyde, C. The experience of spouses caring for a person on home haemodialysis: an ethnography. *Renal Society of Australasia Journal*, 2008;4(3).
38. Ladner, S. Practical ethnography: A guide to doing ethnography in the private sector. 2016, Routledge Press
39. Pole, C. and Hillyard, S., 2015. Doing fieldwork. SAGE.
40. Small, M.L., How many cases do I need?' On science and the logic of case selection in field-based research. *Ethnography*, 2009;10(1), pp.5-38
41. Pelto, P.J. Applied ethnography: Guidelines for field research. 2013 London: Routledge
42. Kelly N, Blake S, Plunkett A. Learning form excellence in healthcare: a new approach to incident reporting. Arch Dis Child 2016;101(9):788-91
43. UK Renal Registry 21st Annual Report 2019– data to 31/12/2017, Bristol, UK.
44. Madden, R. Being ethnographic: A guide to the theory and practice of ethnography. 2010 London: SAGE.42.
45. Hammersley, M. and Atkinson, P. Ethnography: Principles in practice. 2007, Routledge
46. Wind, G.,. Negotiated interactive observation: Doing fieldwork in hospital settings. *Anthropology & Medicine*, 2008;15(2): 79-89.
47. Long, D., Hunter, C. and Van der Geest, S.,. When the field is a ward or a clinic: Hospital ethnography. *Anthropology & Medicine*, 2008;15(2):71-78.
48. Finkler, K., Hunter, C. and Iedema, R. What is going on? Ethnography in hospital spaces. *Journal of Contemporary Ethnography,* 2008;37(2), pp.246-250.
49. Emerson, R.M., Fretz, R.I. and Shaw, L.L. Writing ethnographic fieldnotes. 1995, University of Chicago Press.

50. Ghodsee, K. From notes to narrative: Writing Ethnographies that everyone can read. 2016, University of Chicago Press.
51. Drennan J. Cognitive interviewing: verbal data in the design and pretesting of questionnaires. *Journal of Advanced Nursing*. 2003;42(1):57-63.
52. Collins D. Pretesting survey instruments: an overview of cognitive methods. *Quality of Life Research* 2003;12(3):229-38
53. Paap MCS, Using the Three-Step Test Interview to understand how patients perceive the St. George's Respiratory Questionnaire for COPD patients (SGRQ-C). *Quality of Life Research*. 2016;25(6):1561-70

54. Yardley, L et al (2016). Understanding and promoting effective engagement with digital behavior change interventions. American Journal of Preventive Medicine, 1-28.
55. Beatty PC, et al. Research synthesis: The practice of cognitive interviewing. *Public Opinion Quarterly*. 2007;71(2):287-311
56. Macdonald, Keith. 'Using Documents' in Researching Social Life. Gilbert, Nigel (ed.) 2008, London: SAGE
57. Hseih H-F and Shannon SE. Three approaches to qualitative content analysis. *Qualitative Health Research* 2005;15 (9):1277-1288.
58. Clerke, T. & Hopwood, N. Doing ethnography in teams: A case study of asymmetries in collaborative research. 2014, Springer Science & Business Media.
59. Creese, A. & Blackledge, A. Voice and meaning-making in team ethnography. Anthropology & Education Quarterly, 2012;43(3):306-324.
60. Erickson KC, Stull DD. Doing team ethnography: Warnings and advice. 1998 (Vol. 42) SAGE
61. Greenhalgh, T., Wherton, J., Papoutsi, C., Lynch, J., Hughes, G., Hinder, S., Procter, R. and Shaw, S.,. Analysing the role of complexity in explaining the fortunes of technology programmes: empirical application of the NASSS framework. *BMC Medicine*, 2018;16(1):66.
62. Solis-Trapala, I., Schoenmakers, I., Goldberg, G.R., Prentice, A., Ward, K.A. Sequences of regressions distinguish nonmechanical from mechanical associations between metabolic factors, body composition, and bone in healthy postmenopausal women. *The Journal of Nutrition*, 2016;146: 846-854.
63. Wermuth N, Sadeghi K. Sequences of regressions and their independences.*Test* 2012;21:215–52.
64. Wright S. The method of path coefficients. *Ann Math Stat* 1934;3:161–215.
65. Lawson CA, Solis-Trapala I, Dahlstrom U, et al. Comorbidity health pathways in heart failure patients: A sequences-of-regressions analysis using cross-sectional data from 10,575 patients in the *Swedish Heart Failure Registry*. *PLoS Med* 2018;15(3): e1002540
66. Kalbfleisch JD, Lawless JF. The analysis of panel data under a Markov assumption. *J Am Stat Assoc* 1985;80:863–71.
67. Briggs V, Solis-Trapala I, Wailoo A, McCullough K, Lambie M, Caskey FJ, Fotheringham J, Davies SJ, Wilkie M. United Kingdom Catheter Study - protocol synopsis. *Perit Dial Int*. Vol. 2017;38:113–118
68. Standfield L, Comans T, Scuffham P. Markov modelling and discrete event simulation in health care: a systematic comparison. *Int J Technol Assess Health Care*. 2014;30(2):165-72
69. Walker S, Dixon S, Palmer S, Sculpher M. Getting cost-effectiveness technologies into practice: the value of implementation. EEPRU Reports, Implementation, Innovation
69a. O'Cathain, A., Murphy, E., & Nicholl, J. (2008). The Quality of Mixed Methods Studies in Health Services Research. Journal of Health Services Research & Policy, 13(2), 92–98
70. INTEGRATED group consists of (in alphabetical order), Chan C, Combes G, Davies S, Finkelstein F, Firanek C, Gomez R, Jager KJ, George VJ, Johnson DW, Lambie M, Madero M, Masakane I, McDonald S, Misra M, Mitra S, Moraes T, Nadeau-Fredette AC, Mukhopadhyay P, Perl J, Pisoni R, Robinson B, Ryu DR, Saran R, Sloand J, Sukul N, Tong A, Szeto CC, Van Biesen W. Transition Between Different Renal Replacement Modalities: Gaps in Knowledge and Care-The Integrated Research Initiative. *Perit Dial Int*. 2019;39(1):4-12