Queen's University Belfast

Belfast Health and Social Care Trust

Northern Health and Social Care Trust

ACReDiT

Advance care planning with older patients who have end-stage kidney disease: Feasibility of a deferred entry randomised controlled trial incorporating a mixed methods process evaluation

Randomised Clinical Trial Protocol

NCT02631200

Advance Care Planning with Older Patients Who Have End-stage Kidney Disease

Contents

Figures and Tables

Abbreviations

ACP	Advanced care planning
ADRT	Advance decision to refuse treatment
BHSCT	Belfast Health and Social Care Trust
CORE 34	Clinical Outcomes in Routine Evaluation measure
CRF	Case Report Form
ESKD	End-stage kidney disease
HSCT	Health and Social Care Trust
IST 15	Isaacs Set Test
KDQOL-36™	Kidney Disease Quality of Life instrument
PI	Principal Investigator
RCT	Randomised Clinical Trial
RRT	Renal replacement therapy
SC	Steering committee
SES	Socio-economic status
SHARED	Patient Experience of Shared Decision Making

1. Administrative Information

1.1. Title

Advance care planning with older patients who have end-stage kidney disease: Feasibility of a deferred entry randomised controlled trial incorporating a mixed methods process evaluation.

Trial acronym: ACReDiT

1.2. Trial Registration

ACReDiT (IRAS No 193402)

ClinicalTrials.gov: NCT02631200

1.3. Protocol Version

Version 6.2: September 2016

1.4. Funding

This study is funded by Dunhill Medical Trust. Dunhill Medical Trust has no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

1.5. Roles and Responsibilities

Authors': Peter O'Halloran (PO) [(a)], Helen Noble (HN) [(a)], Kelly Norwood (KN) [(a)], Jackie Boylan (JAB) [(a)], Kevin Brazil (KB) [(a)], Damian Fogarty (DF) [(b)], Joan Brown (JOB) [(b)], Peter Maxwell (PM) [(b)], Joanne Shields (JS) [b)], Robert Mullan (RM) [(c)] Christopher Cardwell (CC) [(d)], Mike Clarke (MC) [(d)], Rachael Morton (RM) [(e)], Fliss Murtagh (FM) [(f)].

a: School of Nursing and Midwifery, Queen's University, Belfast; b: Belfast Health and Social Care Trust; c: Northern Health and Social Care Trust; d: School of Medicine, Dentistry and Biomedical

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Authors' contributions

PO and HN conceived of the study

PO, HN, FM, RM and DF initiated the study design and JOB, JS, PM, RM, KN, and JAB advised on engagement with clinical sites and implementation strategy

RM, PO and JAB planned the economic evaluation

PO, HN, KB, MC and CC are grant holders

CC provided statistical expertise and CC, PO, KN, JOB, and RM will conduct study analyses

All authors contributed to the refinement of the study protocol and approved the final manuscript.

Table 1: Trial Sponsor

Trial Sponsor	Queen's University, Belfast
Sponsor's Reference	B16/06
Contact Name	Mrs Louise Dunlop, Head of Research Governance
Address	Queen's University Belfast, 63 University Road, Belfast BT7 1NF
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Table 2: Roles and Responsibilities

Principal investigator (PI) and Post-Doctoral Research Fellows (PDRFs):	Study design and implementation Preparation of protocol and revisions Preparation of data collection forms and CRFs (case report forms) Recruitment, data collection and completion of CRFs, along with follow up of study patients and adherence to study protocol. Publication of study reports Organising Trial Management Committee (TMC) meetings

	Budget Administration Responsible for trial master file
HSCT local principal investigators	Recruitment of patients Liaising with PI and PDRFs
Steering Committee (SC) **Chairperson: Prof Vivien Coates** **Members: all investigators**	Agreement of final protocol Reviewing study progress Agreeing changes to the protocol and/or investigators' brochures (if necessary) Overseeing management of trial master file
Trial Management Committee (TMC) **Chairperson: Dr Peter O'Halloran** **Members: PDRFs, and other CI's as issues of particular relevance to their expertise are to be discussed, with increased input from the trial statistician during the analysis phase of the trial.**	Expert advice on methodology Study planning Organisation of steering committee meetings Data verification Randomisation
Statistician (Chris Cardwell)	Selection of statistical tests and advice on analyses and interpretation

1.6 Table 3: World Health Organisation Trial Registration Data Set

Data Category	Information
Primary registry and trial identifying number	ClinicalTrials.gov: NCT02631200
Date of registration in primary registry	October 28, 2015
Source(s) of monetary or material support	Dunhill Medical Trust
Primary sponsor	Queen's University Belfast
Contact for public and scientific queries	Dr Peter O'Halloran; p.ohalloran@qub.ac.uk
Public title	Advance Care Planning With Older Patients Who Have End-stage Kidney Disease
Scientific title	Advance Care Planning With Older Patients Who Have End-stage Kidney Disease: Feasibility of a Deferred Entry Randomised Controlled Trial Incorporating a Mixed Methods Process Evaluation
Countries of recruitment	Northern Ireland, United Kingdom
Health condition(s) or problem(s) studied	Advance care planning, kidney failure, chronic
Intervention(s)	Behavioural: Advance care plan
Key inclusion criteria	• Attending the renal units taking part in the study • Receiving renal replacement therapy (RRT) • Capacity to understand, retain, and weigh the necessary information and communicate their decisions • Identified by their consultant as having worsening symptoms, functional decline, and two or more co-morbidities
Key exclusion criteria	• Expected to die in the next three months
Study type	Interventional
Date of first enrolment	December 2016
Target sample size	80 (patients and relative/friends)
Recruitment status	Not yet recruiting
Primary outcome(s)	Quality of life: measured by the Kidney Disease Quality of Life instrument - Short Form (KDQOL-36™)
Key secondary outcomes	• Agreement between the patient and their nominated relative/friend in terms of the patient's preferences: measured by asking the relative/friend to make an independent assessment of the patient's preferences in relation to the key information covered by the ACP intervention, before taking part in the ACP • Depression: measured by the Clinical Outcomes in Routine Evaluation measure (CORE 34) • The degree to which the patient felt that they had shared in decision-making: measured by the Patient Experience of Shared Decision Making (SHARED) instrument

2. Introduction

2.1. Background and Rationale

The prevalence of moderate to severe chronic kidney disease (defined as stages 3-5 CKD) has been estimated at 6-8.5% amongst adults in the UK[1–3] and at over 30% in those aged 75 and over[2]. It is associated with rising risks of hospitalisation, cardiovascular events, cognitive impairment and death[4]. The rapidly growing minority of older patients with CKD who progress to end-stage kidney disease (ESKD) are at even greater risk[5]. However, a substantial proportion of patients and their families do not discuss end-of-life care - including withdrawal of dialysis, ICU admission, involvement of specialist palliative care, cardiopulmonary resuscitation, and place of death – with health professionals[6,7]. Moreover, the high incidence of impaired cognitive capacity amongst patients with ESKD limits their ability to make informed choices and places additional decision-making burdens on their families[8,9]. In this situation, advance care planning can be a useful approach to engaging with the patient and their family to help them think through their preferences for care at the end-of-life, leading to better communication between professionals and patients and their families, and improved decision-making should the patient become incapacitated.

Advance care planning (ACP) has been defined as a process of discussion between an individual, their care providers, and often those close to them, about future care.[10] It may lead to an advance statement of preferences; an advance decision to refuse treatment (ADRT); or to the appointment of someone with lasting power of attorney. ACP can be a complex and challenging process for patients, their families and professionals, raising cultural and personal sensitivities around death[11]; with uptake influenced by a range of social and cultural beliefs, and organisational issues[12]. Nevertheless, emerging evidence suggests ACP can reduce rates of hospital admission, increase use of hospice and palliative care, facilitate the delivery of care that is less aggressive, increase patient and family satisfaction, and reduce anxiety and depression in surviving relatives[11,13–15]. Consequently, in the UK ACP is seen as good practice for those with long-term conditions, or who are at the end of life[16,17]. It is also recognised as a mark of high quality care in CKD and ESKD[18–20].

2.2. Need for a trial

Research into ACP in CKD is limited. A recent systematic review[21] found some evidence that ACP led to increased well-being and reduced anxiety amongst patients and families. However, most studies

were descriptive, and intervention studies measured a limited set of outcomes. Issues for research included:

1) Poor agreement between surrogate decision-makers and patients on end-of-life preferences such as stopping dialysis.
2) Difficulties health professionals and patients have in knowing how and when to discuss end-of-life care.
3) Patients on dialysis may greatly overestimate their life expectancy.

There is also little available data on cost-effectiveness to guide decision makers in allocating resources for ACP[22]. Given that ACP is recognised as good practice and yet is a challenging process, research is needed to address issues in relation to implementation, patients' readiness to engage, conservative treatment, withdrawal of dialysis, quality of life, costs, and patient and family outcomes[23].

Benefits and harm:

Participating patients will have the opportunity to complete an ACP with the support of trained facilitators and peer supporters. Evidence suggests that ACP can reduce rates of hospital admission, increase use of hospice and palliative care, facilitate the delivery of care that is less aggressive, and increase patient and family satisfaction. Use of ACP is also associated with reduced anxiety and depression in surviving relatives and there is also evidence that most patients and relatives find taking part in end-of-life research a positive experience, with satisfaction derived from contributing to research that may help others in the future.

National guidance on implementing ACP recommends that peer education of patients should be included, using expert patients[10]; and this has been used successfully amongst dialysis patients[24]. Older patients with ESKD are suitable for inclusion in an evaluation of ACP amongst older adults because they exhibit the mixture of functional decline and co-morbidity typical of frail older people[5]. Implementation and evaluation of ACPs is challenging,[25] so intervention processes and research methods should be thoroughly tested before larger scale evaluations are attempted. Therefore, following MRC guidance on the evaluation of complex interventions[26], we propose a study to determine the feasibility of a randomised controlled trial (RCT), including a mixed methods process evaluation, to evaluate ACP delivered by professionals (working in partnership with peer supporters), for older patients with ESKD.

2.3. Full Trial Aims and Objectives

The summary objectives for the proposed full trial are stated below so that the relevance of the objectives for the feasibility study can be appreciated.

Full trial objectives:

Primary objective:

- Measure the degree to which implementation of ACP results in desired outcomes for patients with CKD and their families

Secondary objectives:

- Estimate the cost-effectiveness of ACP compared to standard care
- Explain how the process of implementation and the organisational context affect the success or failure of the intervention

2.4. Feasibility Study Aims and Objectives

Aim of the feasibility study: To determine the feasibility of conducting a deferred entry RCT, incorporating a mixed methods process evaluation, to evaluate ACP with patients who have ESKD.

Objectives of the feasibility study*:*

- Acceptability of the intervention to patients, their relatives, and to health professionals (assessed through interview data)
- Optimal systems for delivering ACP, including the recruitment, training and retention of peer educators (assessed through process mapping, interview data, and reflection by the TMC)
- Recruitment, retention and participation rates (assessed through scrutiny of CRFs)
- Effect sizes that might help inform sample-size estimates for a full trial (assessed by measuring numerical differences between immediate and deferred entry groups in terms of all outcome measures)
- Randomisation procedures and participants' willingness to enter a deferred entry trial (assessed by scrutiny of CRFs and interview data)
- The suitability of a twelve-week deferral period and a nine month process evaluation (assessed by scrutiny of effect sizes and interview data)

- The suitability of survey instruments and outcome measures, including sensitivity of the instruments to detect a change in outcomes (assessed by scrutiny of effect sizes and interview data)
- Time needed to collect and analyse data (assessed my scrutiny of CRFs and researcher records of process study data collection and analysis)
- Estimated resource use and costs of delivering ACP and methods for assessing costs, benefits and cost effectiveness in a full trial (assessed through the range of measures detailed below in section 4.2)

Criteria for progression to a full trial: A protocol for a full trial will be developed if the current study findings indicate that:

- The ACP intervention is acceptable to patients, their relative/friends and to health professionals
- Peer educators can be recruited, trained, and retained
- ACP can be readily implemented by relevant staff
- Recruitment, participation, and retention rates are likely to be adequate for a full trial
- The instruments are not excessively burdensome to patients or data collectors, and show acceptable reliability and validity
- An economic evaluation is feasible

3. Methods: Design, setting, participants, interventions and outcomes

3.1. Trial Design

Patients and their nominated relative/friends will be recruited to a deferred entry RCT. A traditional RCT could be unethical as ACP issues would be raised but not followed through with patients in the control group. Consequently, this study incorporates a deferred entry trial, where participants are randomised either to an intervention group or a deferred entry control group, as recommended in guidance published by the Medical Research Council and the National Institute of Health Research (NIHR)[27]. Participants in the deferred entry group have outcomes measured contemporaneously with the immediate entry group but receive the intervention only after trial data collection for the immediate entry group is complete[28]. Patients, their nominated relative/friends and staff participants will be recruited into the process evaluation, which will last for 12 months from enrolment in the study. This will be underpinned by realist evaluation methodology[29], and use qualitative and observational methods, to evaluate issues influencing the success of implementation[30–32].

3.2. Study Setting

Two sites: the Regional Nephrology Unit at Belfast City Hospital, Belfast Health and Social Care Trust (BHSCT) and the Renal Unit at Antrim Area Hospital, Northern HSCT.

3.3. Eligibility Criteria

Eligible patients will be randomised in equal proportions between the immediate and deferred entry groups.

Patient's eligibility criteria:

- English speaking
- Attending the renal units above
- Aged 65 years or more; with ESKD and receiving RRT

- Capacity to understand, retain, and weigh the necessary information in English and communicate their decisions[10]
- Identified by their consultant as having either worsening symptoms, functional decline, or two or more co-morbidities
- Not expected to die in the next three months

Relative/friend eligibility criteria:

- Aged 18 years or older
- Ability to read, write, and speak English
- Identified by the patient as their nominated relative/friend and willing to represent the patient's wishes should they lose decision-making capacity

3.4. Sample size

Forty patient-relative/friend dyads will be recruited onto the trial. Assuming 25% attrition[44], this sample size is thought to provide sufficient numbers to allow feasibility to be estimated, and to offset the bias in estimates of effect size produced by very small samples[45,46].

3.5 Sampling and recruitment

Patients who are already attending the renal units (the Regional Nephrology Unit at Belfast City Hospital, Belfast Health and Social Care Trust (BHSCT) and the Renal Unit at Antrim Area Hospital, Northern HSCT) will be recruited into the study (see below).

Sampling

The sampling frame will be the sampling list of patients obtained from interrogation of the electronic record who appear to meet Stage 1 eligibility criteria as set out in the CRF i.e.

- Attending one of the participating renal units
- Aged 65 or more
- Receiving RRT

The PDRF will split the list by renal unit, and then number patients in an excel file. The two lists of numbers will be sent to Dr Cardwell, who will randomly select 60 numbers from the BCH list and 20 from the AAH list, and then send these numbers back to the PDRF. These numbers will be matched with the sampling list to identify the first 80 patients to be approached to take part.

These patients will be allocated a study ID number by the PDRF, who will also add the study ID to a CRF and print this out.

The PDRF will populate the first page of each CRF (sections 1 and 2) and then pass the CRFs to the ACP nurses in the renal units.

Patient recruitment to the RCT

- Patient screened for stage-one eligibility by the QUB research team (PDRF) (CRF Section 2).
    - Patient may be screened out.

- Patient screened for stage-two eligibility by the ACP Nurse (ACPN) and the patient's consultant (CRF Section 3).
    - Patient may be screened out. CRF passed to the research team.

- ACPN and consultant decide who will make the first approach to the eligible patient.

- ACPN and/or consultant approach the patient to see if they will consider participation (CRF Section 4).
    - Patient may refuse to participate. CRF passed to the research team.

- Patient expresses interest in the study. Given patient and relative information packs and opportunity to discuss the study.

- 2-7 days later, the ACPN follows up with the patient to see if the patient would like to take part (CRF Section 5).
    - Patient refuses to participate. CRF passed to the research team.

- Patient agrees to participate.
    - ACPN checks to see if the patient would like to involve an expert patient in the ACP process (at the ACP discussion, through telephone support, or both).

- Patient and ACPN sign the consent form.
- Consent form passed to the research team

- ACPN checks whether the patient will involve a relative or friend in the ACP process (CRF Section 6a).
    - Patient will not involve a relative/friend. CRF passed to the research team.

- Patient may not yet have decided to involve a relative or friend in the ACP process.
    - ACPN encourages them to speak with a friend or relative and follows up with the patient in the next few days.

- After 3 days/next dialysis session ACPN checks whether the patient will involve a relative or friend in the ACP process (attending the ACP meeting, nominated on the ACP form, or both) (CRF Section 6b).
    - CRF passed to the research team.

- ACP not implemented until baseline data collection, randomisation, and recruitment of relative/friend to the research are completed.

Relative recruitment to the RCT

The initial approach to the relative/friend will be through the patient giving them a 'Relative information pack.' This will make clear that they can act as the patient's nominated relative/friend and decide not take part in the research if they wish.

The relative/friend information will contain the following request:

'If you decide to take part in the research, please do not discuss the details of their plan with the patient until the research starts. This is because we want to see if having an advance care plan makes a difference to the way you discuss these issues together.'

The relative/friend will be invited to express an interest in the research by contacting the research team directly using a dedicated phone number or email address, or a form and reply-paid envelope (CRF Section 8).

If the relative/friend responds to the invitation, the research team will discuss the trial with them and, if they decide to proceed, post or email a consent form to them.

If the patient has indicated that the relative/friend intends to be involved in the ACP process but the relative/friend has not contacted the research team to express an interest in the research, we will send one reminder to the relative/friend through the patient, asking them to consider also taking part in the research.

If they do not respond to this, we will assume they do not wish to take part in the research.

If the relative/friend consents to take part, we will inform them of which group the patient has been randomised to and proceed with data collection accordingly.

We will also ascertain whether they intend to be present for the ACP discussion and inform the ACPN accordingly.

Baseline data collection

Prior to randomisation, recruited patients will be asked to cooperate with baseline data collection, which will include socio-economic status, education, CKD stage, co-morbidities and time since beginning RRT[38,39] (CRF Sections 8-14). We will collect the following data:

Table 4: CRF data collection, source and location

Data	Data source	Data collector	When and where
GP name, address, telephone	Electronic record	Research Fellow	Trust premises
Patient demographic data	Electronic record	Research Fellow	Trust premises
CKD and RRT status	Electronic record	Research Fellow	Trust premises
List and number of co-morbidities	Electronic record	Research Fellow	Trust premises
Educational level	Patient	Research Fellow	During dialysis
Socio-economic status	Patient	Research Fellow	During dialysis
IST 15 CORE 34 KDQOL-36™ SHARED	Patient	Research Fellow	During dialysis

3.6. Randomisation

Patients will be randomised once baseline data collection is complete. The randomisation sequence will use blocks of random sizes (from 2 to 8 which will be unknown to the research team members involved in recruitment) to prevent the research team from predicting the randomisation sequence. The allocations will be concealed using sequentially numbered, opaque, sealed envelopes. These envelopes will be opened sequentially after obtaining all patients' consent and, their names and other details have been written on the appropriate envelope. The use of envelopes and participant allocation will be monitored to ensure that the envelopes are used in the correct sequence.

3.7. Intervention

This will take place in an outpatient context after the patient has been recruited and randomised:

1. Participants will be offered the opportunity to complete an ACP by a nurse trained as an ACP facilitator, who will discuss the process with them using the booklet, "Your life and your

choices: plan ahead," produced by the Northern Ireland Public Health Agency and Macmillan Cancer Support[33]. At this stage, the ACP nurse will ask the participant to complete the 'Record of my wishes' form found in the booklet.

2. One-to-two weeks later, they will complete an ACP document (Advance Care Planning Summary) with the help of the ACP facilitator, working together with trained expert patients who (if the patient wishes) will provide peer support at the time of ACP completion and subsequently by telephone [10,24,34,35], assisted where necessary by the ACP facilitator.
3. The patient's nominated relative/friend will also be invited to take part in the discussion if the patient wishes and the relative/friend agrees.
4. The ACP document will be based on that used within the BHSCT ("A record of my wishes", recently developed by the Northern Ireland Palliative and End of Life Care Implementation Group and based on the booklet, "Your life and your choices: plan ahead"), resulting in the completion of the Advance Care Planning Summary, alongside the identification of a nominated person to help in decision-making as well as the following:

   a) What the patient would like to happen in the future
   b) What the patient would not want to happen
   c) Recording the presence and broad content of an ADRT if it already exists
   d) Preferred place of care at the end-of-life
   e) Special requests

The patient will be encouraged to keep the ACP with them and to make it available to anyone caring for them. A summary of the patient's wishes in the ACP will be kept with their medical notes and copied to their GP, relevant social and community services, and to out-of-hours and ambulance services. The ACP will be reviewed if circumstances change or the patient changes their mind, and in any case after twelve weeks. Participants in the deferred entry group will be offered the intervention twelve weeks after the immediate entry group. ACP implementation will be informed by a realist review of the literature[36] and draw on the Consolidated Framework For Implementation Research,[37] which focuses on intervention characteristics, organisational setting, and the characteristics of the individuals involved.

NB: Patient's normal hospital care is not affected during the trial and they have the right to withdraw at any time.

3.8. Outcome Data collection

RCT outcome measures

1. Quality of life as measured by the Kidney Disease Quality of Life instrument – Short Form (KDQOL-36™)[40]
2. Degree of cognitive impairment as measured by the Isaacs Set Test (IST 15)[41]
3. Degree of anxiety, depression, well-being, functioning and risk as measured by the Clinical Outcomes in Routine Evaluation measure (CORE 34)[42]
4. The degree to which the patient felt that they had shared in decision-making about their care as measured by the Patient Experience of Shared Decision Making (SHARED) instrument[43]
5. Agreement between the patient and their nominated relative/friend in terms of the patient's preferences. We will measure this by asking the carer to make an independent assessment of the patient's preferences in relation to the key information covered by the ACP intervention (a-e above), before taking part in the ACP.
6. An economic evaluation of costs and benefits of the ACP intervention will be conducted utilising data collected from the following sources:
    a. Electronic hospital admissions and outpatient data for each patient
    b. Patient completed cost diaries documenting health and social care resource use
    c. Patient quality of life data using the SF-12 (contained within the (KDQOL-36™)[40]

Resource use will be valued according to appropriate tariffs, allowing comparison of mean costs per patient by group allocation for the 12 week period of the trial.

3.9. Timeline of Trial Outcome Measures

3.9.a. Immediate Entry Group

Baseline/Time 1: Following enrolment and prior to receiving the intervention, patients randomised to the immediate intervention group will complete the IST 15, CORE 34, and KDQOL-36™, and SHARED. Their nominated relative/friend will make an independent assessment of the patient's ACP preferences before the patient receives the information booklet. Subsequently, the patient and (if the patient wishes) the relative/friend will participate in the ACP intervention.

Time 2: At two weeks following the intervention, the patient will complete the CORE 34 and SHARED, and review their ACP. The nominated relative/friend will make a second independent assessment of the patient's preferences.

Time 3: At 12 weeks the patient will again complete CORE 34, KDQOL-36™, and SHARED and both patient and relative/friend will review the ACP and make any desired changes.

3.9.b. Deferred Entry Group

Patients (and their nominated relative/friends) randomised to the deferred entry group will have outcomes measured contemporaneously with the immediate entry group but receive the intervention only after they have completed three sets of data i.e. at 12 weeks following entry to the trial. At 24 weeks the deferred entry group patients will again complete CORE 34, KDQOL-36™, and SHARED and both patient and relative/friend will review the ACP and make any desired changes. The deferred entry group may have more than one ACP review with the ACPN, however data will only be collected from this group at the final review.

Table 5: Schedule of Trial Interventions and Assessments

Time points	**Immediate entry**		**Deferred entry**	
	Patient *****	Relative	Patient*	Relative/friend
$t_{1\ baseline}$	IST 15 CORE 34 KDQOL-36™ SHARED	ACP agreement questionnaire	IST 15 CORE 34 KDQOL-36™ SHARED	
	ACP intervention	ACP intervention		
2/52	ACP 1st review CORE 34 SHARED	ACP agreement questionnaire (before review) ACP review**	CORE 34 SHARED	
12/52	CORE 34 KDQOL-36™ SHARED ACP 2nd review	ACP agreement questionnaire (before review) ACP review**	CORE 34 KDQOL-36™ SHARED	ACP agreement questionnaire
			ACP intervention	ACP intervention
24/52			ACP review**	ACP agreement questionnaire (before

			CORE 34 KDQOL-36™ SHARED	review) ACP review**

Key: IST 15 = Isaacs Set Test
CORE 34 = Clinical Outcomes in Routine Evaluation measure
KDQOL-36™ = Kidney Disease Quality of Life instrument – Short Form
SHARED = Patient Experience of Shared Decision Making instrument
***** Patients in both groups will also complete a cost diary during intervention period as part of the economic evaluation
** Relative/friend may or may not be at the review of the ACP with the patient (this is at the patient and/or relative friend's discretion)

4. Methods: Data Analysis and Management

4.1. Data analysis

4.1.a. Baseline Data

Baseline results will be presented in tables and analysed using a range of descriptive statistics in SPSS for both groups. Categorical variables will be presented as numbers and percentages of those patients who were in the immediate entry group. Continuous variables will include the mean, median, standard deviation and data range.

4.1.b. Statistical Analysis of Trial Data

The proportion of patients eligible for inclusion, agreeing to participate and completing the study will be calculated along with 95% confidence intervals (CIs). Questionnaires (CORE 34, KDQOL-36™, SHARED) will be administered to both the immediate and deferred entry groups, at baseline, 2 and 12 weeks post-intervention (includes immediate entry group only). Analysis of covariance will be used to calculate the mean difference (and 95% CIs) in outcome variables (CORE 34, KDQOL-36™, SHARED) at 12 weeks between the intervention and control group adjusting for baseline values (reference BMJ. 2001 Nov 10; 323(7321): 1123–1124.). Alternatively, Mann-Whitney U tests will be performed on the change from baseline to 12 weeks in the two groups. Further analyses employing paired t-test or Wilcoxon signed rank tests, will be conducted to compare changes in outcome measures within the immediate entry and deferred entry groups. Statistical analyses will employ the $p<0.05$ significance level. Investigation of the pattern of missing data (e.g. missing completely at random, missing at random, missing not at random) which will help determine the appropriate method for handling the missing data. For quality of life data, a weighted mean value for the group

sample may be used to 'fill in' the missing items. Depending on the amount of missing data, multiple imputation will be considered."

4.2. Economic Evaluation

4.2.a. Outline of the economic analysis

The feasibility of a cost-effectiveness and cost-utility analysis of the ACP intervention compared to usual care, conducted from a societal perspective, will be explored in the pilot study, to inform a full economic evaluation alongside the main trial.

4.2.b. Outcomes for the analysis

The analysis will report the cost per [primary endpoint achieved e.g. relative/friend agreement or SHARED]; and the cost per quality adjusted life year (QALY) gained of the ACP intervention compared to usual care.

4.2.c. Participant utilities

The SF-6D preference based instrument contained within the SF-12 and KDQoL-36 survey will be administered to all patient participants at baseline and 12 weeks. QALY weights (utilities with a value between 0 and 1) from self-reported data will be calculated using UK tariffs (the value set) of the SF-6D. QALYs will be calculated by multiplying the utility with the time spent in that health state using an area under the curve approach. A minimally important difference in utility has been reported at 0.03-0.05. Mean costs (including volume of resource use) and mean health outcomes per allocated group will be reported with 95% confidence intervals. Mean costs will be presented as unadjusted and adjusted for any baseline differences in age, sex, or SES.

4.2.d. Detailed Statistical Analysis of Economic Data

Skewed cost data: Cost data are likely to be right skewed as they are bounded by zero (i.e. can't be negative); have no upper bound, and a small number of patients may incur very high costs, affecting

the mean. The cost distribution will be plotted in a histogram and non-parametric bootstrapping will be used for analysis.

Results: The mean and total volume of major categories of resource use (e.g. hospitalisations; doctor's visits; nurse visits;) will be reported for each group. The difference in the volume of resource use for each group and 95% confidence intervals for the difference will be reported.

Total costs: The total cost will be calculated by multiplying the arithmetic mean cost by the number of participants in each group. Mean costs with standard deviations and total costs for each group will be reported in UK pounds for the most recent reference year. The difference in total costs will be assessed using the student t test and/or analysis of variance (ANOVA). Total costs will also be adjusted for relevant baseline characteristics (e.g. age, sex).

Benefits will include: (i) quality of life, measured at baseline and 12 weeks with the KDQOL-36™ survey; (ii) the proportion of participants with a unit increase in CORE 34; (iii) the proportion of patients with a unit increase in either SHARED or relative/friend Agreement – [whichever will be the primary outcome] (iv) QALY gained at 12 weeks.

Sensitivity analyses: One-way sensitivity analyses will be conducted around key variables including health and social care costs +/- individual patient costs; and health system resource use as measured in patient diaries compared to the base case measurement using hospital administrative records.

4.3. ACP process Evaluation

Participants will be followed for 12 months (or until bereavement, if earlier) from enrolment in the study.

Five focus groups will be conducted with HSCT staff (see below), to elicit their experience of ACP and their views on barriers and facilitators of implementation. Staff will be recruited based on their close involvement in the ACP process and identified and contacted

1. Four intervention facilitators

2. Four peer supporters

3. Four members of medical staff

4. Four members of nursing/AHP staff

5. Those training staff in ACP

Staff will be recruited based on their close involvement in the ACP process. Initially, they will be identified and contacted by co-investigators employed in the participating HSC Trusts.

Interviews will also be conducted with 4 patients and their nominated relative/friends to examine their experiences of ACP 12-weesk post-intervention. Researcher's will also observe staff training for ACP; carry out documentary analysis; and develop a process map[47] of the personnel and systems involved in managing ACP.

4.3.a. Outcome Measures from the Process Evaluation

The proportion of patients who die during the study will be recorded. This will include whose end of life wishes were complied with, as measured by a comparison of their ACP and the record of the circumstances of their death in their medial notes, and in a survey of bereaved nominated relative/friends, carried out at least 3 months after their death.

We will compare relative/friends, whose relative experienced care broadly in alignment with their wishes, with relative/friends of those who did not, in terms of their satisfaction with care, as measured by the After-Death Bereaved Family Interview[48] and level of depression measured by the Patient Health Questionnaire (POQ9)[49].

4.4. Analysis of observational data

Interviews will be digitally recorded and transcribed verbatim. Each piece of interview and other data will be coded according to the initial theory derived from CFIR and the realist review to allow indexing and retrieval in a suitable database. The documentary evidence, process map, and interview transcripts will be reviewed searching for configurations that support, contradict and link theory, seeking to explain outcomes.

4.5. Overall Outcomes and Outputs

Immediate outcome of this study will be an appraisal of the feasibility of a full study, with an analysis of the factors crucial to successful implementation of ACP, paving the way for a future definitive evaluation of the impact of ACP on the well-being of patients with complex co-morbidities and their

families, and identification of the key factors leading to successful implementation. The full study will evaluate the impact of ACP on patients who have ESKD and on associated costs, with anticipated benefits of greater adherence to their wishes at the end of life; reduced rates of hospital admission; greater use of hospice and palliative care services; less anxiety and depression; increased perception of shared decision-making; and greater well-being, and physical and social functioning. Relative/friends should experience greater agreement with patients' wishes, greater satisfaction with care, and less depression on bereavement.

4.6. Data Management

Patients will only be identifiable by their participant code – all identifying personal information will be stored in a locked filing cabinet, in a locked room. Access to study data will be restricted to the minimum number of individuals necessary for quality control and analysis – the PI and the researchers. Outside of the direct care team, only the PI and the researchers will have access to participants' personal data. A password system will be utilised to control access and passwords will be changed on a regular basis. Participant files are to be stored in numerical order and will be retained in storage for a period of 5years following study completion. Digital data will be stored on a password protected central server accessed through a password protected computer at the School of Nursing and Midwifery, Queen's University. Belfast. Checks will be applied at the time of data entry into a specific field and before the data is written (committed) to the database. Data will be analysed by members of the research team in Queen's University Belfast, Kings College London, and (in the case of data for the economic evaluation) the University of Sydney. All data will be anonymised before it is transferred or analysed. We will use the secure 'DropBox' facility provided by Queen's University to transfer password protected data files. Hard copies of documents containing research data will be stored in a locked filing cabinet in a locked room at the School of Nursing and Midwifery. Only PO will have access to this data. Tapes from interviews and focus groups will be destroyed after the data has been transcribed and recorded verbatim. Researchers will send weekly email reports to the PI with any information on missing data, missing forms, and missing visits.

5. Ethics and dissemination

Research Ethics has been granted from QUB research governance and from Belfast and Northern Trusts. Any amendments to the protocol which may affect the conduct of the study, benefits to patients, including changes to the study design, study objectives, patient population and sample sizes, procedural details will require a formal amendment to REC body. Informed consent for both participants and patients will be obtained by ACP nurses on both sites. All trial-related information will be stored securely at the Medical Biology Centre, Queen's University, Belfast (please see 4.6 for further information). Governance of the study will be guided by a Trial Management Committee and a Steering Committee. The Trial Management Committee will meet at least monthly and will oversee day-to-day aspects of the trial. It will be chaired by the PI, Dr O'Halloran, and include the two PDRF, and other CI's as issues of particular relevance to their expertise are to be discussed, with increased input from the trial statistician during the analysis phase of the trial. The Trial Steering Committee will be chaired by Professor Vivien Coates (Professor of Nursing Research, University of Ulster) and will comprise the PI and all the CI. It will meet in full face to face twice during the trial and there will also be two other meetings, which might take place by teleconference. The two face-to-face meetings will be near the beginning and the end of the funding period, to approve the final set-up plans for the trial and to consider the findings, prepare a publication and other dissemination activities, and plan the main trial and its funding application. The Trial Steering Committee will determine whether or not the trial has met the criteria to show that a main trial is feasible. The PI's and CI's have no competing interests to share for the overall trial and each study site.

6. Appendices

Appendix 1: Patient consent forms

Appendix 2: Study Information sheets

Appendix 3: Case report forms

Appendix 4: Questionnaires

Appendix 5: Cost diaries; resource use case report forms

Appendix 5: Consultant initial approach to patient script

First approach by a consultant or ACPN to a patient who may take part in the ACP (ACREDIT) study

INTRODUCTION

- Hello, Mr/Mrs…….. my name is ……
- I'm here to ask if you would consider helping us with some research we are doing?
- You don't have to make up your mind right away.
- But if it's OK with you, I'll tell you the basics now – is that all right?
- Then, if you are interested, I'll ask one of the nurses to give you the details so you can make up your mind about whether you want to take part.

~

EXPLANATION

- We want to do some research into something called 'advance care planning.'
- Have you heard of that?
- Advance care planning is where you discuss your options and choices for future care with your doctors and nurses.
- This means we know about what you would like to happen if your condition gets worse and we can try and make sure things work out as you would wish.
- You can also include your relatives in the advance care planning if you want to.

~

INVITATION

- We want to do some research about this so that we can see how well advance care planning works for patients and their relatives.
- As I say, you don't have to make your mind up now.
- But if you think you might be interested in taking part I'll ask the nurse to come and speak with you and give you some more details.
- Would you be interested in finding out a bit more?

~

PATIENT SAYS YES

- Thank you.
- I'll ask the nurse to come and talk to you and give you some more details.
- If you have any questions then please do ask me or one of the nurses.

~

PATIENT SAYS NO

- That's perfectly all right. We won't bother you again about it.
- But if you have any questions, or if you change your mind and think you might want to take part, just speak to me or to the nurse in charge.
- Thanks for discussing it with me.

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