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ABSTRACT

Introduction: Shared treatment decision-making and comprehensive planning of care are fundamental in advanced chronic kidney disease (CKD) management. For older patients, decision-making is challenging. There is a paucity of data on several key outcomes for this population including survival, quality-of-life, symptom burden, changes in physical functioning, and experienced burden of healthcare. Patients, caregivers and clinicians consequently face significant uncertainty when making life-impacting treatment decisions. The Elderly Advanced CKD Program includes quantitative and qualitative studies to better understand and address challenges in treatment decision-making and planning of care among this increasingly prevalent elderly cohort.

Methods and analysis: The primary component of the program is a multi-centre prospective observational cohort study that will enrol 800 patients aged ≥75 years with kidney failure (estimated glomerular filtration rate ≤15 mL/min/1.73m^2). Patients entered are in the decision-making phase or have recently made a decision on preferred treatment. Planned treatment will be recorded (dialysis, conservative kidney management or undecided) in addition to other baseline characteristics. Patients will be prospectively followed until death or a maximum of 4 years, with the primary outcome being survival. Secondary outcomes are receipt of short-term acute dialysis, receipt of long-term maintenance dialysis, changes in biochemistry, and end-of-life care characteristics. The central aim is to prospectively capture clinical outcomes and formulate a risk prediction tool applicable for use in the decision-making phase. A subset of patients and caregivers will be enrolled into nested sub-studies that will longitudinally assess quality-of-life, symptom burden, and burden of care. Additional qualitative interview work will explore patient and caregiver experiences of treatment decision-making processes and of the care received.

Ethics and dissemination: This program has ethics approval through the Sydney Local Health District Human Research Ethics Committee (2019/ETH07718, 2020/ETH02226, 2021/ETH01020, 2019/ETH07783). Final results of this work will be disseminated through peer-reviewed journals and presented at scientific meetings.

STRENGTHS & LIMITATIONS OF THIS PROGRAM

The Elderly Advanced CKD Program will;

- Provide a wide-ranging assessment of important clinical outcomes for older patients with kidney failure, including survival, quality of life, symptom burden, receipt of dialysis, receipt of conservative kidney management, caregiver experiences, and end-of-life care,
- Use a combination of quantitative and qualitative methodologies,
- Evaluate the considerations, processes and challenges of treatment decision-making from a patient and carer-centred perspective,
- Include a prospective observational cohort design with large sample size, multi-centre enrolment and ease of data collection, to derive a risk prediction model to aid in shared treatment decision-making.

A limitation of the program is that it is being conducted across multiple sites in Australia and extrapolation of findings to healthcare settings beyond this should be done with caution.

BACKGROUND

Introduction

Chronic kidney disease (CKD) has risen from the 17th to the 12th leading cause of death globally over the last 25 years. Increasing numbers of individuals are progressing to the most advanced form of the disease, kidney failure (defined as an estimated glomerular filtration rate 15 mL/min/1.73 m^2 or lower) (1). For the increasing proportion of these patients with advanced age and multi-morbidity, complex decisions need to be made about treatment with kidney replacement therapy (KRT, with dialysis or kidney transplantation) or conservative kidney management (CKM). CKM involves a range of interventions to manage symptoms, improve quality of life, delay progression and manage complications, without the use of KRT.

In Australia, the prevalent dialysis population increased from 337 to 549 per million population between 2000 to 2019, with over half of prevalent patients aged ≥65 years and 26% aged ≥75 years (2). Whilst dialysis registries in many countries measure entry onto dialysis well, it is more challenging to quantify and understand the characteristics and outcomes of older patients with kidney failure who do not enter dialysis programs. A retrospective data linkage analysis combined deaths ascribed to kidney failure from the Australian National Death Index with the Australia and New Zealand Dialysis and Transplant Registry and identified 21,370 patients with death due to kidney failure over a 4-year period. Roughly half of the patients studied received dialysis (n=10,949) and a similar proportion died without ever receiving dialysis (n=10,421). The majority of the patients who did not receive dialysis were aged ≥75 years (3), the age group which also has the highest rate of incident dialysis in Australia and other developed countries.

For older patients with advanced CKD, the processes of decision-making between treatment pathways differ from that of younger patients, where there are clear differences in survival between treatment options. The greatest uncertainty occurs for patients aged 75 years or older, where few patients are medically suitable for transplantation, and there is limited data to inform decision-making, especially around the relative burden of dialysis and CKM and the outcomes they deliver for an older patient group. In turn, there are few tools to assist clinicians, patients and caregivers in making decisions between these treatment pathways (4-9). Best practice approaches to decision-making between treatment pathways should be timely, well-informed and individualised (10). Timely decisions are essential, as patients who commence dialysis in an unplanned manner have increased mortality (11, 12), reduced quality of life (13), and significantly higher healthcare costs (14). Ideally, an understanding of the various health outcomes important to older patients, including survival, quality of life, symptom burden, and experienced burden of healthcare should be at the centre of discussions (15-17). Furthermore, patients express a desire for frank, detailed prognostic information (18-20) but, in practice, there is little data to inform such prognostication. Real-world decision-making is thus challenging and highly variable.

Current knowledge of outcomes

Prospective clinical data collection is difficult in older patients, most notably seen in their under-representation in randomised clinical trials (21, 22). This reflects their high burden of comorbidities and frailty, high rates of cognitive impairment, and high experienced burden of treatment (23). Well-designed observational studies can

achieve high inclusivity, external validity, and feasibility, and hold significant applicability for evaluating outcomes among older advanced CKD patients. A scoping review of published observational literature reporting outcomes relevant to shared decision-making for older patients with kidney failure identified 248 publications, the majority from high-income English-speaking countries (USA, UK, Canada and Australia) and published in the last 10 years (6). However, 77% of studies exclusively pertained to patients on dialysis (6), similar to that seen in reported meta-analyses (24, 25) and highlights the limited published evidence base of CKM (9).

A meta-analysis of patient survival among elderly patients with kidney failure from studies between 1976 to 2014 reported similar 1-year survival rates between dialysis and CKM (73.0-78.4% and 70.6%, respectively) (24). However, survival estimates for CKM patients were derived from only 12 of the total 89 studies and accounted for much fewer patients (724 vs. 294,196 for CKM and dialysis, respectively). There was also considerable residual heterogeneity for survival estimates within each treatment group, which may reflect changes in patterns of referral, acceptance onto dialysis programs and components of CKM provided by centres over the long period of the review. Other recent observational studies have been inconsistent, with some suggesting a survival advantage with dialysis (26, 27), and others suggesting limited or no survival advantage from dialysis in those patients with severe comorbidity, poor performance status or extreme age (28-30).

Many of these survival comparisons are also confounded by methodological issues (24, 31) such as; lead-time bias, immortal time bias, and indication bias. Lead-time bias arises from variability in defining a distinct starting point for CKM. This may result in a perceived survival advantage in CKM patients if their survival time is calculated from an earlier starting point that is not an equivalent of when dialysis would have been initiated. Conversely, immortal time bias occurs mainly in analysis of retrospective cohorts, when an index starting point is defined and patients go on to start dialysis much later (or not at all), giving rise to a perceived survival advantage ascribed to dialysis treatment. Indication bias is inherent to analysing survival in elderly kidney failure cohorts where there is expected referral of healthier patients for dialysis, and referral of older and frailer patients for CKM. Incorporating baseline covariates such as frailty and functional status into adjusted survival analyses aims to account for this, however such data is frequently not collected or available. These biases are magnified in retrospective analyses conducted after treatment decisions have been made, and notably 71 of the 89 included studies in Foote et al.'s systematic review were retrospective (24).

A range of other outcomes are important to patients, caregivers and clinicians in decision making, including quality of life, symptom burden, functional independence, experienced burden of healthcare and caregiver burden. Existing literature suggests that the health-related quality of life of older patients on dialysis, compared

to CKM, is broadly similar (32), that some older advanced CKD patients would 'trade-off' survival time in preference for maintaining functional independence (33-35), and that dialysis initiation is associated with high rates of deterioration of physical functioning among patients and high caregiver burden (36-38). Additionally, Canadian and UK studies suggest older dialysis patients spend significantly more time in hospital than CKM patients (26, 39). However, there are notable limitations to this data, as few studies have broad and systematic data collection, resulting in high risk of selection bias and limited adjustment for other variables (32). The majority of published studies are cross-sectional, and longitudinal repeated measures of data across either treatment pathway are lacking. Furthermore, patient outcomes, burden of healthcare and caregiver experiences are markedly dependent on healthcare structures. There is a need to assess these outcomes widely, including in the Australian context.

Program aims

In response to these limitations in data, we describe a program of work, the Elderly Advanced CKD Program, designed to explore decision-making and planning of care for older patients (defined in this program as age ≥75 years) with kidney failure. This includes addressing deficiencies in outcome data, broadening understanding of patient priorities, and applying this evidence to better support real-world decision-making processes. The aims of this study program are:

(a) To quantify survival in a large cohort of older patients with kidney failure followed from estimated glomerular filtration rate (eGFR) ≤15mL/min/1.73m^2,
(b) To formulate a risk prediction tool for mortality applicable to patients at the time of treatment decision-making,
(c) To quantify other key patient outcomes among older patients with kidney failure in a prospective and longitudinal fashion, including quality of life, symptom burden, burden of planned and unplanned hospitalisations, and caregiver burden,
(d) To qualitatively explore patient and caregiver experiences of shared decision-making processes, planning of care, CKM and, ultimately, end-of-life care.

METHODS AND ANALYSIS

Program design

The program consists of 4 components (*Figure 1*); a prospective observational cohort study with 3 components (including a small qualitative component), and a purely qualitative study examining patient and caregiver experiences:

1. OUTcomes Of Older patients with Kidney failure (OUTLOOK),

2. Treatment modalities for the InfirM ElderLY with end stage kidney disease (TIMELY),
3. Caregivers of The InfirM ElderLY with end stage kidney disease (Co-TIMELY), including a small qualitative component, and
4. CONsumer views of Treatment options for Elderly patieNts with kiDney failure (CONTEND).

Study design

OUTLOOK is a multi-centre prospective observational cohort study that aims to enrol 800 older patients with kidney failure (age ≥75 years and eGFR ≤15mL/min/1.73m^2). The study is ethically approved with a waiver of the need for individual patient consent. TIMELY is a nested cohort study that aims to enrol a subset of 150 patients within OUTLOOK, which requires individual patient consent for additional data collection relating to quality of life, symptom burden and functional status over time. The Co-TIMELY study aims to enrol 100 caregivers of older patients to prospectively examine caregiver responsibilities, quality of life and caregiver burden.

Study population and recruitment

Inclusion and exclusion criteria for OUTLOOK, TIMELY and Co-TIMELY are shown in *Table* 1. Patients are enrolled into OUTLOOK by study investigators if they meet the inclusion criteria, which are broad to minimise selection bias, maximise recruitment and increase external validity of the study. An eGFR ≤15mL/min/1.73m^2, as calculated by the Chronic Kidney Disease Epidemiology Collaboration formula, was chosen to define kidney failure, as it reflects a point at which patients and clinicians would be expected to be making decisions regarding planning for dialysis or CKM (4). This uniform definition provides an index date from which survival time will be determined for all participants, regardless of treatment pathway, aiming to mitigate lead-time bias and immortal time bias.

All patients enrolled into OUTLOOK will be screened for potential participation in TIMELY, with the only additional exclusion criteria for patient participation being extreme infirmity, significant cognitive impairment or insufficient English language skills (see *Table 1*), all of which would preclude participation in patient-reported outcome questionnaires. Potential TIMELY participants will be approached, and if willing to participate, will be asked to provide written informed consent. For the Co-TIMELY study, patients who consent to participate in TIMELY will be asked to nominate a primary caregiver. This caregiver will be screened against inclusion/exclusion criteria (see *Table 1*) and, if eligible, will be approached for participation with a view to provide written informed consent.

Table 1. Inclusion and exclusion criteria for OUTLOOK, TIMELY and Co-TIMELY.

Inclusion criteria	**Exclusion criteria**
Patient age ≥ 75 years	Patient is receiving dialysis at the time of initial screening
Patient eGFR ≤ 15mL/min/1.73m^2	Patient not expected to survive 3 months beyond enrolment

Additional caregiver criteria for Co-TIMELY: - Nominated by the patient as a primary caregiver	Additional exclusion criteria for patients in TIMELY and for caregivers in Co-TIMELY: - Extreme infirmity (as assessed study team) - Significant cognitive impairment (inability to complete questionnaires as assessed by the treating nephrologist or study team, with a guiding lower threshold of ≤18 on mini-mental state examination) - English language skills insufficient to participate in questionnaires

eGFR, estimated glomerular filtration rate; OUTLOOK, OUTcomes Of Older patients with Kidney failure; TIMELY, Treatment modalities for the InfirM ElderLY with end stage kidney disease; Co-TIMELY, Caregivers of The InfirM ElderLY with end stage kidney disease.

Study period

Patients enrolled into OUTLOOK have baseline data collection and will be prospectively followed until death or for a maximum of 4 years, with follow-up occurring at 6-monthly intervals. Similarly, participants enrolled into TIMELY will be followed until death or for a maximum of 4 years, with follow-up questionnaires completed by participants at 12-monthly intervals. Caregivers enrolled into Co-TIMELY will be followed prospectively until either caregiver death, until 6 months after death of the corresponding care-recipient, or for a maximum of 4 years.

Measurement of baseline characteristics

Baseline data collection schedules for OUTLOOK, TIMELY and Co-TIMELY are shown in *Table* 2. OUTLOOK will only collect data from patient medical records and from healthcare providers involved in patient care (including from public/private hospitals, general practitioners, specialist records, and pathology providers). At enrolment, site investigators will review records and discuss with the treating team to determine the patient's planned treatment pathway (dialysis, CKM, or undecided) and the approximate timing of this decision.

Other baseline data collection incorporates wide-ranging measurement of patient characteristics that, based on prior literature, may influence the study's primary outcome of survival. These include patient demographics, medical history, medications, baseline pathology measurements, measures of functional status, and treatment plans. Baseline medical history will be used to derive a modified Charlson comorbidity score, a validated predictor of mortality in kidney failure patients, with a theoretical maximum score of 37 (40, 41). Baseline pathology measurements include serum creatinine, eGFR, albumin, haemoglobin, parathyroid hormone, and proteinuria (albumin:creatinine ratio or protein:creatinine ratio), all of which are markers of kidney disease progression (17). Measures of functional status are the Clinical Frailty Scale (42), Karnofsky performance score (43), and mobility status. The Clinical Frailty Scale is a 9-point scale that was chosen for its feasibility and its prior use in advanced CKD research showing an association with mortality (44). The Karnofsky functional performance score assesses functional status on a scale of 0 to 100, and it is the most widely used measure of functional impairment in chronic disease states including kidney failure (45). Additional treatment-related questions at baseline address the use of advance care planning, appointment of an enduring guardian, and the 'surprise question', which asks the treating nephrologist if they would be surprised if the patient died in the next 12 months and has demonstrated predictive ability for mortality in advanced CKD (46).

For TIMELY participants, two additional cognitive and nutritional baseline components will be collected during face-to-face visits. The mini-mental state examination (47) is a validated tool for assessment of cognition in the general population (48), and cognitive impairment (score of <24 out of a maximum score of 30) is associated with adverse health outcomes in advanced CKD (45). The subjective global assessment tool (49) assesses gastrointestinal symptoms, weight change, functional capacity and visual evaluation of subcutaneous tissue and muscle mass. It is the most commonly used nutritional assessment tool in Australian nephrology units, with higher rating scores associated with increased mortality in dialysis patients (50).

For caregivers participating in Co-TIMELY, baseline data includes caregiver demographics, caregiver characteristics (including relationship to the care-recipient and duration of caregiving), and caregiver responsibilities.

Table 2. Study schedule for data collection. 'O' denotes data collection for both OUTLOOK & TIMELY, 'T' denotes data collection for TIMELY only, and 'C' denotes data collection for Co-TIMELY only.

	Timeline based on individual date of enrolment								
Data collection	**Baseline**	**6 mths**	**1 yr**	**18 mths**	**2 yrs**	**30 mths**	**3 yrs**	**42 mths**	**4 yrs**
Demographics (age, gender, ethnicity, primary language, marital status, residential status)	O								
Medical history (Charlson comorbidity score, medications)	O								
Functional status (Clinical Frailty Scale, Karnofsky Performance Score, mobility)	O								
Treatment pathway decision (dialysis, CKM, undecided), advance care planning status, surprise question	O								
Biochemistry	O	O	O	O	O	O	O	O	O
Survival status (including date, location and cause of death)		O	O	O	O	O	O	O	O
Receipt of dialysis		O	O	O	O	O	O	O	O
Cognitive assessment (MMSE)	T								
Nutritional status (SGA)	T								
Patient questionnaires: - Quality of life (EQ-5D, SWLS) - Symptom burden (iPOS-Renal)	T		T		T		T		T
Patient-reported changes in living situation, mobility and functional status	T		T		T		T		T
Patient-reported hospitalisations	T		T		T		T		T
Caregiver demographics (age, gender, ethnicity, primary language, education level)	C								
Caregiver characteristics (relationship to care recipient, duration of caregiving)	C								
Caregiver responsibilities	C		C		C		C		C
Caregiver questionnaires: - Quality of life (EQ-5D) - Caregiver burden (Zarit Burden Interview)	C		C		C		C		C
Data linkage (National Death Index, ANZDATA, Admitted Patient Data Collection, MBS, PBS)									O/T

OUTLOOK, OUTcomes Of Older patients with Kidney failure; TIMELY, Treatment modalities for the InfirM ElderLY with end stage kidney disease; Co-TIMELY, Caregivers of The InfirM ElderLY with end stage kidney disease; CKM, conservative kidney management; MMSE, mini-mental state examination; SGA, subjective global assessment; EQ-5D, Euroqol-5

Dimension; SWLS, Satisfaction with Life Scale; ANZDATA, Australian and New Zealand Dialysis and Transplant Registry; MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Scheme.

Primary and secondary outcomes

The primary outcome of OUTLOOK is survival. Secondary outcomes are receipt of short-term acute dialysis, receipt of long-term maintenance dialysis, changes in biochemistry (including serum creatinine and eGFR), and characteristics of end-of-life care (including date, location, and primary cause of death).

In the nested sub-study TIMELY, additional outcomes are changes in health-related quality of life, changes in symptom burden, and patient-reported hospitalisations in the preceding 12 months. Health-related quality of life is assessed at baseline and in annual follow-up by the EuroQol-5 Dimension 3-Level (EQ-5D-3L) questionnaire and the Satisfaction with Life Scale (SWLS). The EQ-5D-3L is a generic quality of life measure assessing 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) (51). These responses can be compared against an Australian EQ-5D value set (52) to derive a single utility score ranging from less than 0 to 1 (with 0 representing death, negative values representing utilities worse than death and 1 representing perfect health). The SWLS is a 5-item scale with questions relating to ideal life, conditions of life, and satisfaction with present and past life (53). It has been used in various disease states including advanced CKD (32). Symptom burden is assessed with the Integrated Palliative Care Outcome Scale (iPOS-Renal), an inventory modified for use in advanced CKD populations (32, 54). It asks the responder about the impact of 15 kidney disease-specific physical symptoms and further emotional symptoms (each rated on a 5-point scale from 0, no impact, to 4, overwhelming impact) in the preceding week.

In the caregiver study Co-TIMELY, primary outcomes are changes in caregiver quality of life and changes in caregiver burden. Varied tools have been used to assess caregiver quality of life in prior CKD studies and the optimal tool is unclear (55). Baseline and annual caregiver quality of life is assessed in Co-TIMELY with the EQ-5D and SWLS as these are generic measures and they align with the TIMELY study. Caregiver burden is assessed at baseline and annual follow-up using the Zarit Burden Interview, a 12-question tool relating to feelings of personal strain from the caregiving role, with 5 responses for each question ranging from 0 (never) to 4 (almost always) (56). This tool is the most commonly used measure of subjective caregiver burden in advanced CKD studies (55).

Following study completion, study datasets will be linked to the National Death Index, Australian and New Zealand Dialysis and Transplant Registry (ANZDATA), Admitted Patient Data Collection (APDC), and Medicare and Pharmaceutical Benefits Schedules (MBS, PBS), using relevant national and state-based data linkage entities. Data linkage will be used to assess inpatient and non-inpatient healthcare usage and costs, dialysis characteristics and end-of-life care characteristics across treatment pathways.

Data analysis plan

From OUTLOOK, differences in survival between treatment groups will be analysed using Kaplan-Meier survival analysis and log-rank tests. A multivariable Cox proportional hazards model will be constructed using

prespecified covariates based on clinical plausibility with the aim of selecting a parsimonious model. Primary analyses will be a complete case analyses, however a multiple imputation approach for missing values of predictors will be assessed according to the proportion and patterns of missingness. Model performance will be assessed using standard metrics including discrimination (C-statistic) and calibration (Hosmer-Lemeshow statistic), and internal validation will be performed with bootstrap resampling.

Bayesian networks allow a more flexible modelling approach, are more reliable when there are high correlations between predictor variables and allow a more efficient method to handle missing data, so an additional Bayesian network will be formulated using data from OUTLOOK. This model will consist of a target variable (mortality), multiple random variables (nodes), probabilistic dependencies between variables, and conditional probability tables that describe the direction and degree of influence between variables. The Bayesian model's performance will be assessed using the area under the curve-receiver operating characteristic (AUCROC), which is analogous to the C-statistic derived from the multivariate Cox proportional hazards model. Prediction models will be reported according to transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines (57).

Further data from TIMELY and Co-TIMELY including longitudinal changes in patient and caregiver quality of life, symptom burden, caregiver burden, and additional data from data linkage for end-of-life care characteristics, healthcare usage and costs will be analysed using a hierarchical modelling approach, which accounts for within- and between-patient variability for continuous outcomes, and Chi-square tests and logistic regression for categorical outcomes.

Sample size calculation

To guide sample size calculations in OUTLOOK, we estimated 40-50% 2-year mortality in patients who go on to dialysis and 60% for CKM patients (11). A minimum of 10 events per candidate variable is used as a benchmark for sample size calculations in model development studies. It is anticipated that 6-10 variables will be included in our final models based upon prior advanced CKD risk prediction models (58-61). However, larger sample sizes mitigate the risk of model overfitting, improve precision and performance of models, and enhance clinical utility (62). Accordingly, a sample size of 800 patients in OUTLOOK is targeted, with a target of 150 patients participating in TIMELY and 100 caregivers participating in Co-TIMELY.

Qualitative methodology

Caregivers in Co-TIMELY whose care-recipient is specifically receiving CKM will be asked to participate in a qualitative component. Minimum sample size is 20 caregivers and maximum sample size will be determined from data saturation, whereby no new themes are emerging from participant interviews. Single-encounter interviews will be conducted face-to-face or via teleconferencing for 30-60 minutes. These will be semi-structured using an interview guide, with participants asked to discuss their experiences of the planning of care, daily roles as a caregiver of a patient receiving CKM, and the impact being a caregiver has had on their life. Caregivers of patients who die during the study, who indicated on their consent that they are willing participate in a post-death interview, will be approached no sooner than 3 months and no later than 6 months after their

care-recipient's death to participate in a second semi-structured interview exploring end-of-life care. Target sample size for this end-of-life care component is 10 caregivers. Questions will be based on the Quality of Dying and Death (QoDD) tool (63, 64). Example interview questions include whether their care recipient was comfortable, how often end-of-life symptoms were controlled, whether they were at peace with dying, where they died, and what support was offered to the caregiver.

CONTEND is the final qualitative component of the program and involves single-encounter interviews with patients ≥70 years with kidney failure (eGFR ≤15mL/min/1.73m^2) and their caregivers. Eligible patients must have had a discussion about treatment pathways with their nephrologist and they are about to decide or have made a treatment decision within the last 2 years (ie. patients can be on dialysis or a CKM pathway initiated within 2 years). Patients and caregivers will be purposefully recruited during routine outpatient visits. The focus of CONTEND is upon decision-making, with a broad interview guide including questions on what information was provided to facilitate decision-making, experiences of the decision-making process, barriers/enablers of decision-making, and experiences of end-of-life care planning. This component aims for a minimum of 20 patients and 20 caregivers and maximum sample size determined from data saturation.

Transcripts from the Co-TIMELY qualitative component and from CONTEND will be thematically analysed using grounded theory, where data will be coded using NVivo software and abstract categories are constructed inductively to identify themes and relationships between themes. Data will be reported according to the consolidated criteria for reporting qualitative research (COREQ) (65).

Patient and public involvement statement

The design of this research program is shaped by prior literature on older patient priorities when making advanced CKD treatment decisions (4). The program began as pilot studies in 2017, with initial enrolment at 3 hospital sites. Informed by feedback from patients and caregivers, small changes to study design have been made to improve feasibility. The study design and participant information sheets for these studies will continue to receive regular feedback from the George Institute for Global Health Consumer Engagement Panel, consisting of patients with kidney disease and their caregivers.

ETHICS AND DISSEMINATION

OUTLOOK is approved as a waiver of individual patient consent study in accordance with the 2018 National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (66). All other study components in this program involve direct patient contact and data collection beyond routine care, and accordingly involve written and informed consent. All study data is stored through a dedicated electronic data capture tool only accessible to site and central investigators. All data is managed confidentially and anonymously, and will be stored for a minimum of 15 years in accordance with national guidelines (66). The results of this research are intended to be disseminated through peer-reviewed journals and presented at scientific meetings.

DISCUSSION

While there will always be some degree of prognostic uncertainty in patient care (67), the Elderly Advanced CKD Program aims to provide clinicians, patients and caregivers with accurate data and tools to reduce the extent of this uncertainty in the planning and provision of care for older patients with kidney failure. To our knowledge, this is the first study to prospectively follow an older kidney failure cohort to produce a risk prediction model for survival for use in the treatment decision-making phase. The nested work with patients and caregivers will provide detailed and longitudinal insights on important patient-reported outcomes such as quality of life and experienced burden of healthcare.

In the context of the exponential increase in elderly patients progressing to kidney failure in developed countries, this study program holds high clinical relevance. The program is currently enrolling across 6 sites in Australia, with the intention of further expansion to achieve enrolment targets and national representation. Baseline data from the 316 patients currently enrolled in OUTLOOK has found the following characteristics: mean age mean 83.5 years (range 75-95 years), predominantly community-dwelling (88%), and high prevalence of frailty (58%) and functional impairment (46% requiring a mobility aid). This is the population group in whom there is greatest equipoise regarding whether dialysis compared with CKM offers greater benefits. This work will thus generate valuable outcome data and ensure that the developed risk prediction tool will have direct clinical application. However, we acknowledge that such quantitative data alone will not overcome all challenges in complex decision-making. Accordingly, this research program incorporates qualitative work, to broaden the focus and encompass perspectives of patients and their families on treatment decision-making processes, experiences of CKM and end-of-life care.

Large multi-centre cohorts prospectively investigating outcomes in older patients with kidney failure are few. To date, there are two comparative studies. The European QUALity study (EQUAL) is an ongoing study recruiting patients ≥65 years with eGFR ≤20mL/min/1.73m^2 in 5 European countries, with prospective follow-up for 4 years (68). EQUAL aims to evaluate optimal timing of dialysis initiation among older patients, with additional insights regarding survival and longitudinal changes in patient-reported outcomes. Over 1500 of the targeted 3500 participants have been enrolled. The focus is on dialysis planning and the investigators have stated that patients on a CKM pathway will not be captured (69). The Canadian Frailty Observation and Interventions Trial (CanFIT) is a multi-centre observational cohort study which has enrolled 603 adult patients between 2012-2018 with eGFR <30mL/min who have had baseline frailty assessments and are being prospectively followed. CanFIT aims to examine the longitudinal trajectory of frailty and its associations with morbidity, mortality and patient-reported outcomes, but is capturing patients with less advanced kidney disease compared with those in the Australian Elderly Advanced CKD Program. Nonetheless, both EQUAL and CanFIT complement the large-scale, robust and prospective aims of the OUTLOOK study. The collective aims of these studies, particularly those of the Elderly Advanced CKD Program, are to better inform discussions and decision-making processes for older patients with advanced kidney disease.

This work has limitations. Given the observational methodology, there is the potential for confounding from measured and unmeasured variables in the quantitative components of this program. While the study design aims to minimise the impact of lead-time and immortal time bias, complete elimination of these biases is not possible. Furthermore, while the study program aims to achieve multi-centre national representation, application of findings beyond Australia will have limitations.

CONCLUSION

Decision-making between treatment pathways is highly complex for older patients with kidney failure, their caregivers and clinicians. Challenges include accurate outcome predictions, communicating meaningful prognostic information, communicating associated uncertainty, and using this information to undertake systematic processes of shared decision-making and planning of care. The Elderly Advanced CKD Program is a large-scale multi-centre research program designed to address modifiable factors relating to each of these challenges by using prospective and robust data, collected efficiently at a national level; to derive the necessary tools for patients, caregivers and clinicians; and, to understand patient and caregiver preferences for care. Such work is novel, practice-informing and much needed, as we face a growing population of elderly, frail and comorbid kidney failure patients.

AUTHORS' CONTRIBUTIONS

CF, MG, AS, NG and YM conceived the Elderly Advanced CKD Program and formulated protocols for study components. AS drafted the protocol manuscript, and NG, AM, CL, KY, YM, JR, GDT, CG, IA, SR, VN, CF and MG contributed to critical review and revisions of the manuscript.

COLLABORATORS

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COMPETING INTERESTS

None declared.

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FIGURES

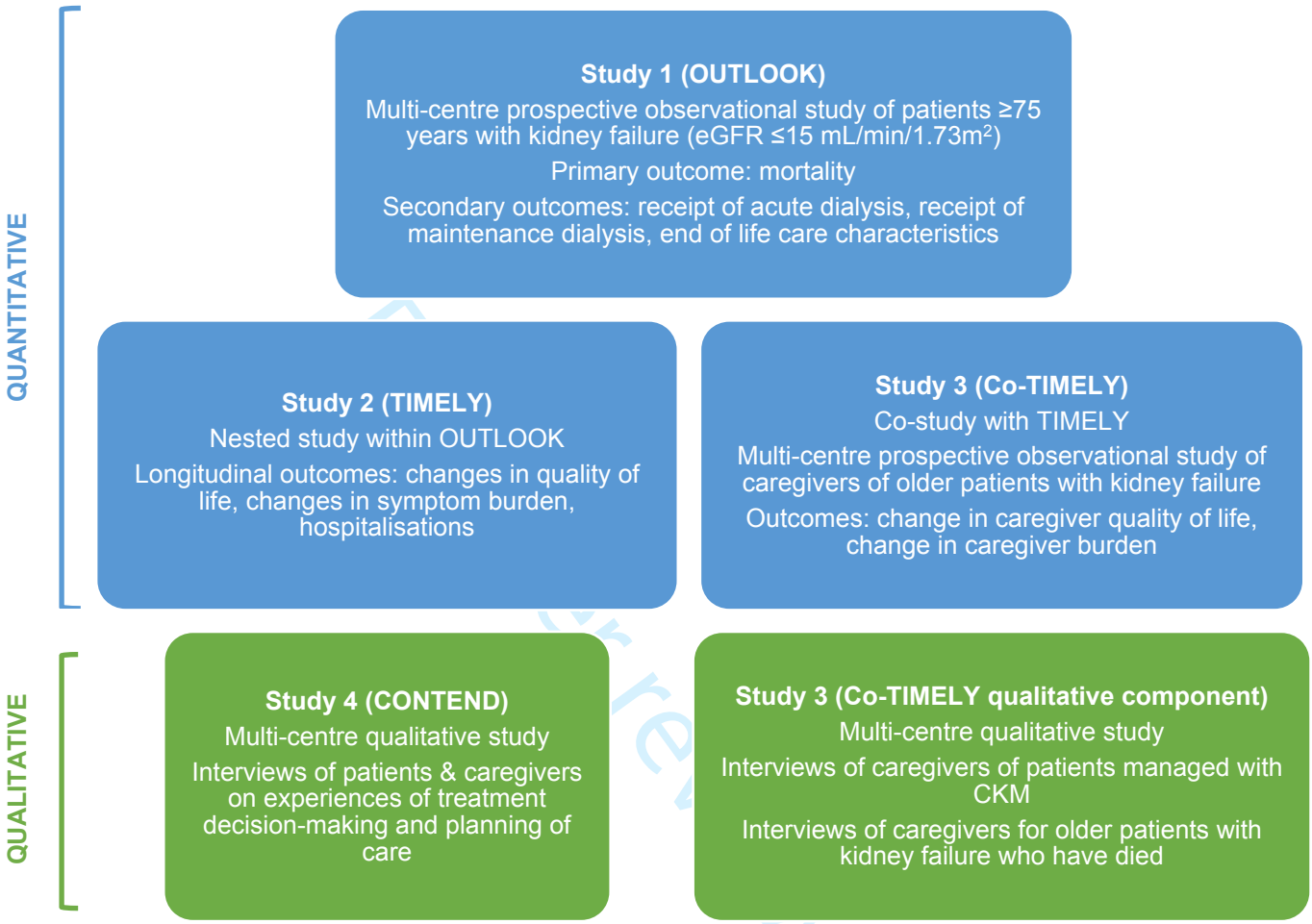
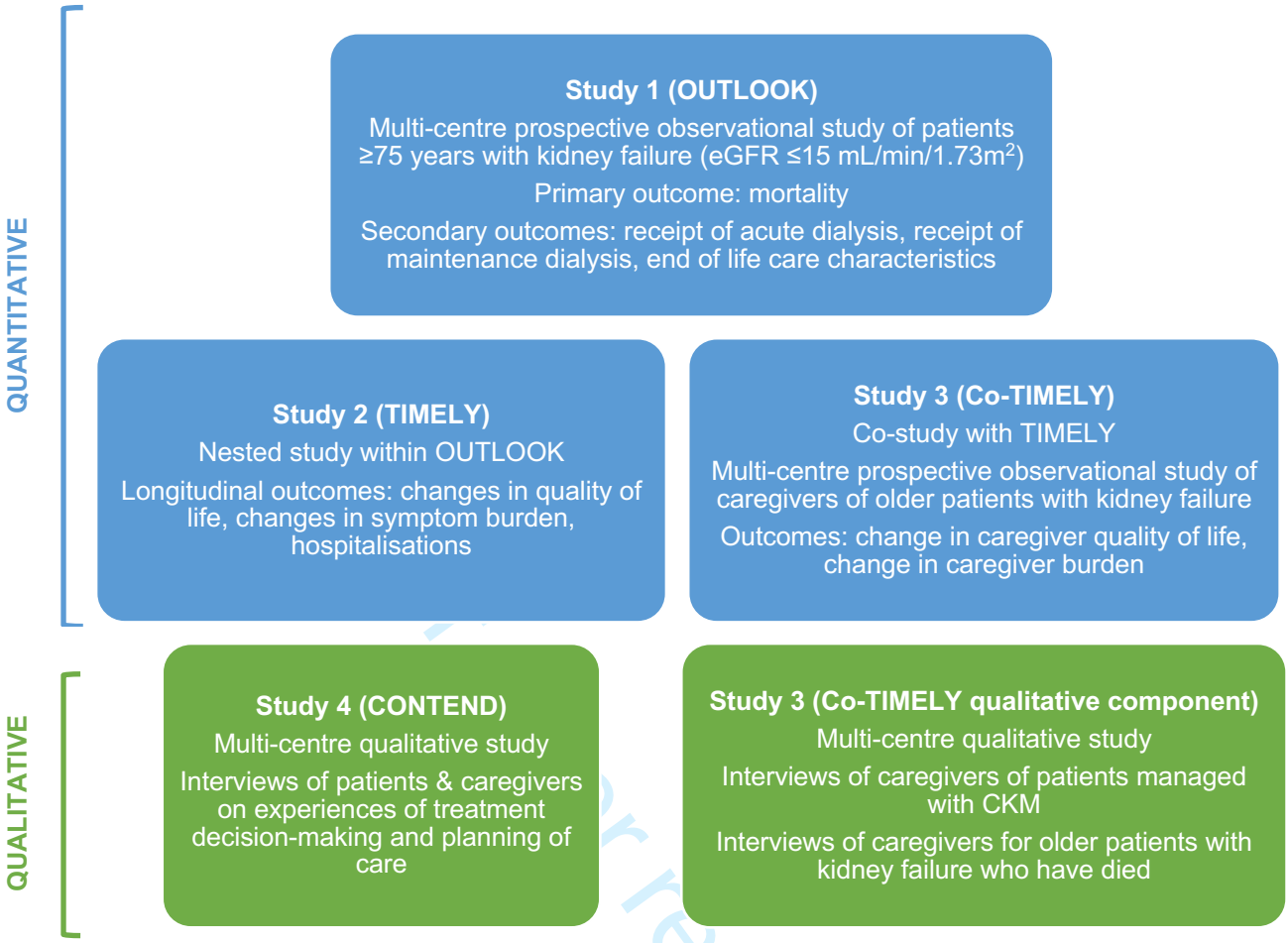


Figure 1. Components of the ELDERLY Program.

eGFR, estimated glomerular filtration rate; CKM, conservative kidney management; OUTLOOK, OUTcomes of Older patients with Kidney failure; TIMELY, Treatment modalities for the InfirM ElderLY with end stage kidney disease; Co-TIMELY, Caregivers of The InfirM ElderLY with end stage kidney disease; CONTEND, CONsumer views of Treatment options for Elderly patieNts with kiDney failure.



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TREATMENT DECISION-MAKING & CARE AMONG OLDER ADULTS WITH KIDNEY FAILURE: PROTOCOL FOR A MULTICENTRE, PROSPECTIVE OBSERVATIONAL COHORT STUDY WITH NESTED SUB-STUDIES AND LINKED QUALITATIVE RESEARCH (THE ELDERLY ADVANCED CKD PROGRAM)

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TREATMENT DECISION-MAKING & CARE AMONG OLDER ADULTS WITH KIDNEY FAILURE: PROTOCOL FOR A MULTICENTRE, PROSPECTIVE OBSERVATIONAL COHORT STUDY WITH NESTED SUB-STUDIES AND LINKED QUALITATIVE RESEARCH (THE ELDERLY ADVANCED CKD PROGRAM)

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ABSTRACT

Introduction: Shared treatment decision-making and planning of care are fundamental in advanced chronic kidney disease (CKD) management. There is limited data on several key outcomes for the elderly population including survival, quality-of-life, symptom burden, changes in physical functioning, and experienced burden of healthcare. Patients, caregivers and clinicians consequently face significant uncertainty when making life-impacting treatment decisions. The Elderly Advanced CKD Program includes quantitative and qualitative studies to better address challenges in treatment decision-making and planning of care among this increasingly prevalent elderly cohort.

Methods and analysis: The primary component is OUTLOOK, a multi-centre prospective observational cohort study that will enrol 800 patients ≥75 years with kidney failure (estimated glomerular filtration rate ≤15mL/min/1.73m^2) across a minimum of 6 sites in Australia. Patients entered are in the decision-making phase or have recently made a decision on preferred treatment (dialysis, conservative kidney management or undecided). Patients will be prospectively followed until death or a maximum of 4 years, with the primary outcome being survival. Secondary outcomes are receipt of short-term acute dialysis, receipt of long-term maintenance dialysis, changes in biochemistry, and end-of-life care characteristics. Data will be used to formulate a risk prediction tool applicable for use in the decision-making phase. The nested sub-studies TIMELY and Co-TIMELY will longitudinally assess quality-of-life, symptom burden, and caregiver burden among 150 patients and 100 caregivers, respectively. CONTEND is an additional qualitative study that will enrol a minimum of 20 patients and 20 caregivers to explore experiences of treatment decision-making and care.

Ethics and dissemination: Ethics approval was obtained through Sydney Local Health District Human Research Ethics Committee (2019/ETH07718, 2020/ETH02226, 2021/ETH01020, 2019/ETH07783). OUTLOOK is approved to have waiver of individual patient consent. TIMELY, Co-TIMELY and CONTEND participants will provide written informed consent. Final results will be disseminated through peer-reviewed journals and presented at scientific meetings.

STRENGTHS & LIMITATIONS OF THIS STUDY

- Prospective study design with large sample size, multi-centre enrolment and ease of data collection.
- Clinical outcome data collection to allow formulation of a risk prediction tool for use in the treatment decision-making phase.
- Nested sub-studies using a combination of quantitative and qualitative methodologies to provide wide-ranging assessment of important clinical outcomes for older patients with kidney failure, including survival, quality of life, symptom burden, receipt of dialysis, receipt of conservative kidney management, caregiver experiences, and end-of-life care.
- The study program is conducted across multiple sites in Australia and extrapolation of findings to other healthcare settings may not be applicable.

INTRODUCTION

Background

Chronic kidney disease (CKD) has risen from the 17th to the 12th leading cause of death globally over the last 25 years. Increasing numbers of individuals are progressing to the most advanced form of the disease, kidney failure (defined as an estimated glomerular filtration rate 15 mL/min/1.73 m^2 or lower) (1). For the increasing proportion of these patients with advanced age and multi-morbidity, complex decisions need to be made about treatment with kidney replacement therapy (KRT, with dialysis or kidney transplantation) or conservative kidney management (CKM). CKM involves a range of interventions to manage symptoms, improve quality of life, delay progression and manage complications, without the use of KRT.

In Australia, the prevalent dialysis population increased from 337 to 549 per million population between 2000 to 2019, with over half of prevalent patients aged ≥65 years and 26% aged ≥75 years (2). Whilst dialysis registries in many countries measure entry onto dialysis well, it is more challenging to quantify and understand the characteristics and outcomes of older patients with kidney failure who do not enter dialysis programs. A retrospective data linkage analysis combined deaths ascribed to kidney failure from the Australian National Death Index with the Australia and New Zealand Dialysis and Transplant Registry and identified 21,370 patients with death due to kidney failure over a 4-year period. Roughly half of the patients studied received dialysis (n=10,949) and a similar proportion died without ever receiving dialysis (n=10,421). The majority of the patients who did not receive dialysis were aged ≥75 years (3), the age group which also has the highest rate of incident dialysis in Australia and other developed countries.

For older patients with advanced CKD, the processes of decision-making between treatment pathways differ from that of younger patients, where there are clear differences in survival between treatment options. The greatest uncertainty occurs for patients aged 75 years or older, where few patients are medically suitable for transplantation, and there is limited data to inform decision-making, especially around the relative burden of dialysis and CKM and the outcomes they deliver for an older patient group. In turn, there are few tools to assist clinicians, patients and caregivers in making decisions between these treatment pathways (4-9). Best practice approaches to decision-making between treatment pathways should be timely, well-informed and individualised (10). Timely decisions are essential, as patients who commence dialysis in an unplanned manner have increased mortality (11, 12), reduced quality of life (13), and significantly higher healthcare costs (14). Ideally, an understanding of the various health outcomes important to older patients, including survival, quality of life, symptom burden, and experienced burden of healthcare should be at the centre of discussions (15-17). Furthermore, patients express a desire for frank, detailed prognostic information (18-20) but, in practice, there is little data to inform such prognostication. Real-world decision-making is thus challenging and highly variable.

Current knowledge of outcomes

Prospective clinical data collection is difficult in older patients, most notably seen in their under-representation in randomised clinical trials (21, 22). This reflects their high burden of comorbidities and frailty, high rates of cognitive impairment, and high experienced burden of treatment (23). Well-designed observational studies can

achieve high inclusivity, external validity, and feasibility, and hold significant applicability for evaluating outcomes among older advanced CKD patients. A scoping review of published observational literature reporting outcomes relevant to shared decision-making for older patients with kidney failure identified 248 publications, the majority from high-income English-speaking countries (USA, UK, Canada and Australia) and published in the last 10 years (6). However, 77% of studies exclusively pertained to patients on dialysis (6), similar to that seen in reported meta-analyses (24, 25) and highlights the limited published evidence base of CKM (9).

A meta-analysis of patient survival among elderly patients with kidney failure from studies between 1976 to 2014 reported similar 1-year survival rates between dialysis and CKM (73.0-78.4% and 70.6%, respectively) (24). However, survival estimates for CKM patients were derived from only 12 of the total 89 studies and accounted for much fewer patients (724 vs. 294,196 for CKM and dialysis, respectively). There was also considerable residual heterogeneity for survival estimates within each treatment group, which may reflect changes in patterns of referral, acceptance onto dialysis programs and components of CKM provided by centres over the long period of the review. Other recent observational studies have been inconsistent, with some suggesting a survival advantage with dialysis compared to CKM (26, 27), and others suggesting limited or no survival advantage from dialysis in those patients with severe comorbidity, poor performance status or extreme age (28-30).

Many of these survival comparisons are also confounded by methodological issues (24, 31) such as; lead-time bias, immortal time bias, and indication bias. Lead-time bias arises from variability in defining a distinct starting point for CKM. This may result in a perceived survival advantage in CKM patients if their survival time is calculated from an earlier starting point that is not an equivalent of when dialysis would have been initiated. Conversely, immortal time bias occurs mainly in analysis of retrospective cohorts, when an index starting point is defined and patients go on to start dialysis much later (or not at all), giving rise to a perceived survival advantage ascribed to dialysis treatment. Indication bias is inherent to analysing survival in elderly kidney failure cohorts where there is expected referral of healthier patients for dialysis, and referral of older and frailer patients for CKM. Incorporating baseline covariates such as frailty and functional status into adjusted survival analyses aims to account for this, however such data is frequently not collected or available. These biases are magnified in retrospective analyses conducted after treatment decisions have been made, and notably 71 of the 89 included studies in Foote et al.'s systematic review were retrospective (24).

As identified in qualitative and discrete choice studies, a range of other outcomes are important to older patients, caregivers and clinicians in decision making, including quality of life, symptom burden, functional independence, experienced burden of healthcare and caregiver burden (32-35). Existing literature suggests that

the health-related quality of life of older patients on dialysis, compared to CKM, is broadly similar (36), that some older advanced CKD patients would 'trade-off' survival time in preference for maintaining functional independence (32-34), and that dialysis initiation is associated with high rates of deterioration of physical functioning among patients and high caregiver burden (37-39). Additionally, Canadian and UK studies suggest older dialysis patients spend significantly more time in hospital than CKM patients (26, 40). However, there are notable limitations to this data, as few studies have broad and systematic data collection, resulting in high risk of selection bias and limited adjustment for other variables (36). The majority of published studies are cross-sectional, and longitudinal repeated measures of data across either treatment pathway are lacking. Furthermore, patient outcomes, burden of healthcare and caregiver experiences are markedly dependent on healthcare structures. There is a need to assess these outcomes widely, including in the Australian context.

Program aims

In response to these limitations in data, we describe a program of work, the Elderly Advanced CKD Program, designed to explore decision-making and planning of care for older patients (defined in this program as age ≥75 years) with kidney failure. This includes addressing deficiencies in outcome data, broadening understanding of outcomes that are a priority to patients and caregivers, and applying this evidence to better support real-world decision-making processes. The aims of this study program are:

(a) To quantify survival in a large cohort of older patients with kidney failure followed from estimated glomerular filtration rate (eGFR) ≤15mL/min/1.73m^2,
(b) To formulate a risk prediction tool for mortality applicable to patients at the time of treatment decision-making,
(c) To quantify other key patient outcomes among older patients with kidney failure in a prospective and longitudinal fashion, including quality of life, symptom burden, burden of planned and unplanned hospitalisations, and caregiver burden,
(d) To qualitatively explore patient and caregiver experiences of shared decision-making processes, planning of care, CKM and, ultimately, end-of-life care.

METHODS AND ANALYSIS

Program design

The program consists of 4 components (*Figure 1*); a prospective observational cohort study with 3 components (including a small qualitative component), and a purely qualitative study examining patient and caregiver experiences:

1. OUTcomes Of Older patients with Kidney failure (OUTLOOK),

2. Treatment modalities for the InfirM ElderLY with end stage kidney disease (TIMELY),
3. Caregivers of The InfirM ElderLY with end stage kidney disease (Co-TIMELY), including a small qualitative component, and
4. CONsumer views of Treatment options for Elderly patieNts with kiDney failure (CONTEND).

Study design

OUTLOOK is a multi-centre prospective observational cohort study that aims to enrol 800 older patients with kidney failure (age ≥75 years and eGFR ≤15mL/min/1.73m^2) across a minimum of 6 sites in Australia. The study is ethically approved with a waiver of the need for individual patient consent. TIMELY is a nested cohort study that aims to enrol a subset of 150 patients within OUTLOOK, which requires individual patient consent for additional data collection relating to quality of life, symptom burden and functional status over time. The Co-TIMELY study aims to enrol 100 caregivers of older patients to prospectively examine caregiver responsibilities, quality of life and caregiver burden.

Study population and recruitment

Inclusion and exclusion criteria for OUTLOOK, TIMELY and Co-TIMELY are shown in *Table* 1. Patients are enrolled into OUTLOOK by study investigators if they meet the inclusion criteria, which are broad to minimise selection bias, maximise recruitment and increase external validity of the study. An eGFR ≤15mL/min/1.73m^2, as calculated by the Chronic Kidney Disease Epidemiology Collaboration formula, was chosen to define kidney failure, as it reflects a point at which patients and clinicians would be expected to be making decisions regarding planning for dialysis or CKM (4). This uniform definition provides an index date from which survival time will be determined for all participants, regardless of treatment pathway, aiming to mitigate lead-time bias and immortal time bias.

All patients enrolled into OUTLOOK will be screened for potential participation in TIMELY, with the only additional exclusion criteria for patient participation being extreme infirmity, significant cognitive impairment or insufficient English language skills (see *Table 1*), all of which would preclude participation in patient-reported outcome questionnaires. Potential TIMELY participants will be approached, and if willing to participate, will be asked to provide written informed consent. For the Co-TIMELY study, patients who consent to participate in TIMELY will be asked to nominate a primary caregiver. This caregiver will be screened against inclusion/exclusion criteria (see *Table 1*) and, if eligible, will be approached for participation with a view to provide written informed consent.

Table 1. Inclusion and exclusion criteria for OUTLOOK, TIMELY and Co-TIMELY.

Inclusion criteria	**Exclusion criteria**
Patient age ≥ 75 years	Patient is receiving dialysis at the time of initial screening
Patient eGFR ≤ 15mL/min/1.73m^2	Patient not expected to survive 3 months beyond enrolment

Additional caregiver criteria for Co-TIMELY: - Nominated by the patient as a primary caregiver	Additional exclusion criteria for patients in TIMELY and for caregivers in Co-TIMELY: - Extreme infirmity (as assessed study team) - Significant cognitive impairment (inability to complete questionnaires as assessed by the treating nephrologist or study team, with a guiding lower threshold of ≤18 on mini-mental state examination) - English language skills insufficient to participate in questionnaires

eGFR, estimated glomerular filtration rate; OUTLOOK, OUTcomes Of Older patients with Kidney failure; TIMELY, Treatment modalities for the InfirM ElderLY with end stage kidney disease; Co-TIMELY, Caregivers of The InfirM ElderLY with end stage kidney disease.

Study period

Patients enrolled into OUTLOOK have baseline data collection and will be prospectively followed until death or for a maximum of 4 years, with follow-up occurring at 6-monthly intervals. Similarly, participants enrolled into TIMELY will be followed until death or for a maximum of 4 years, with follow-up questionnaires completed by participants at 12-monthly intervals. Caregivers enrolled into Co-TIMELY will be followed prospectively until either caregiver death, until 6 months after death of the corresponding care-recipient, or for a maximum of 4 years.

Measurement of baseline characteristics

Baseline data collection schedules for OUTLOOK, TIMELY and Co-TIMELY are shown in *Table* 2. OUTLOOK will only collect data from patient medical records and from healthcare providers involved in patient care (including from public/private hospitals, general practitioners, specialist records, and pathology providers). At enrolment, site investigators will review records and discuss with the treating team to determine the patient's planned treatment pathway (dialysis, CKM, or undecided) and the approximate timing of this decision.

Other baseline data collection incorporates wide-ranging measurement of patient characteristics that, based on prior literature, may influence the study's primary outcome of survival. These include patient demographics, medical history, medications, baseline pathology measurements, measures of functional status, and treatment plans. Baseline medical history will be used to derive a modified Charlson comorbidity score, a validated predictor of mortality in kidney failure patients, with a theoretical maximum score of 37 (41, 42). Baseline pathology measurements include serum creatinine, eGFR, albumin, haemoglobin, parathyroid hormone, and proteinuria (albumin:creatinine ratio or protein:creatinine ratio), all of which are markers of kidney disease progression (17). Measures of functional status are the Clinical Frailty Scale (43), Karnofsky performance score (44), and mobility status. The Clinical Frailty Scale is a 9-point scale that was chosen for its feasibility and its prior use in advanced CKD research showing an association with mortality (45). The Karnofsky functional performance score assesses functional status on a scale of 0 to 100, and it is the most widely used measure of functional impairment in chronic disease states including kidney failure (46). Additional treatment-related questions at baseline address the use of advance care planning, appointment of an enduring guardian, and the 'surprise question', which asks the treating nephrologist if they would be surprised if the patient died in the next 12 months and has demonstrated predictive ability for mortality in advanced CKD (47).

For TIMELY participants, two additional cognitive and nutritional baseline components will be collected during face-to-face visits. The mini-mental state examination (48) is a validated tool for assessment of cognition in the general population (49), and cognitive impairment (score of <24 out of a maximum score of 30) is associated with adverse health outcomes in advanced CKD (46). The subjective global assessment tool (50) assesses gastrointestinal symptoms, weight change, functional capacity and visual evaluation of subcutaneous tissue and muscle mass. It is the most commonly used nutritional assessment tool in Australian nephrology units, with higher rating scores associated with increased mortality in dialysis patients (51).

For caregivers participating in Co-TIMELY, baseline data includes caregiver demographics, caregiver characteristics (including relationship to the care-recipient and duration of caregiving), and caregiver responsibilities.

Table 2. Study schedule for data collection. 'O' denotes data collection for both OUTLOOK & TIMELY, 'T' denotes data collection for TIMELY only, and 'C' denotes data collection for Co-TIMELY only.

	Timeline based on individual date of enrolment								
Data collection	**Baseline**	**6 mths**	**1 yr**	**18 mths**	**2 yrs**	**30 mths**	**3 yrs**	**42 mths**	**4 yrs**
Demographics (age, gender, ethnicity, primary language, marital status, residential status)	O								
Medical history (Charlson comorbidity score, medications)	O								
Functional status (Clinical Frailty Scale, Karnofsky Performance Score, mobility)	O								
Treatment pathway decision (dialysis, CKM, undecided), advance care planning status, surprise question	O								
Biochemistry	O	O	O	O	O	O	O	O	O
Survival status (including date, location and cause of death)		O	O	O	O	O	O	O	O
Receipt of dialysis		O	O	O	O	O	O	O	O
Cognitive assessment (MMSE)	T								
Nutritional status (SGA)	T								
Patient questionnaires: - Quality of life (EQ-5D, SWLS) - Symptom burden (iPOS-Renal)	T		T		T		T		T
Patient-reported changes in living situation, mobility and functional status	T		T		T		T		T
Patient-reported hospitalisations	T		T		T		T		T
Caregiver demographics (age, gender, ethnicity, primary language, education level)	C								
Caregiver characteristics (relationship to care recipient, duration of caregiving)	C								
Caregiver responsibilities	C		C		C		C		C
Caregiver questionnaires: - Quality of life (EQ-5D) - Caregiver burden (Zarit Burden Interview)	C		C		C		C		C
Data linkage (National Death Index, ANZDATA, Admitted Patient Data Collection, MBS, PBS)									O/T

OUTLOOK, OUTcomes Of Older patients with Kidney failure; TIMELY, Treatment modalities for the InfirM ElderLY with end stage kidney disease; Co-TIMELY, Caregivers of The InfirM ElderLY with end stage kidney disease; CKM, conservative kidney management; MMSE, mini-mental state examination; SGA, subjective global assessment; EQ-5D, Euroqol-5

Dimension; SWLS, Satisfaction with Life Scale; ANZDATA, Australian and New Zealand Dialysis and Transplant Registry; MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Scheme.

Primary and secondary outcomes

The primary outcome of OUTLOOK is survival. Secondary outcomes are receipt of short-term acute dialysis, receipt of long-term maintenance dialysis, changes in biochemistry (including serum creatinine and eGFR), and characteristics of end-of-life care (including date, location, and primary cause of death).

In the nested sub-study TIMELY, additional outcomes are changes in health-related quality of life, changes in symptom burden, and patient-reported hospitalisations in the preceding 12 months. Health-related quality of life is assessed at baseline and in annual follow-up by the EuroQol-5 Dimension 3-Level (EQ-5D-3L) questionnaire and the Satisfaction with Life Scale (SWLS). The EQ-5D-3L is a generic quality of life measure assessing 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) (52). These responses can be compared against an Australian EQ-5D value set (53) to derive a single utility score ranging from less than 0 to 1 (with 0 representing death, negative values representing utilities worse than death and 1 representing perfect health). The SWLS is a 5-item scale with questions relating to ideal life, conditions of life, and satisfaction with present and past life (54). It has been used in various disease states including advanced CKD (36). Symptom burden is assessed with the Integrated Palliative Care Outcome Scale (iPOS-Renal), an inventory modified for use in advanced CKD populations (36, 55). It asks the responder about the impact of 15 kidney disease-specific physical symptoms and further emotional symptoms (each rated on a 5-point scale from 0, no impact, to 4, overwhelming impact) in the preceding week.

In the caregiver study Co-TIMELY, primary outcomes are changes in caregiver quality of life and changes in caregiver burden. Varied tools have been used to assess caregiver quality of life in prior CKD studies and the optimal tool is unclear (56). Baseline and annual caregiver quality of life is assessed in Co-TIMELY with the EQ-5D and SWLS as these are generic measures and they align with the TIMELY study. Caregiver burden is assessed at baseline and annual follow-up using the Zarit Burden Interview, a 12-question tool relating to feelings of personal strain from the caregiving role, with 5 responses for each question ranging from 0 (never) to 4 (almost always) (57). This tool is the most commonly used measure of subjective caregiver burden in advanced CKD studies (56).

Following study completion, study datasets will be linked to the National Death Index, Australian and New Zealand Dialysis and Transplant Registry (ANZDATA), Admitted Patient Data Collection (APDC), and Medicare and Pharmaceutical Benefits Schedules (MBS, PBS), using relevant national and state-based data linkage entities. Data linkage will be used to assess inpatient and non-inpatient healthcare usage and costs, dialysis characteristics and end-of-life care characteristics across treatment pathways.

Data analysis plan

From OUTLOOK, differences in survival between treatment groups will be analysed using Kaplan-Meier survival analysis and log-rank tests. A multivariable Cox proportional hazards model will be constructed using

prespecified covariates based on clinical plausibility, including age, gender, comorbidity score, frailty score and functional performance score, with the aim of selecting a parsimonious model. Primary analyses will be a complete case analyses, however a multiple imputation approach for missing values of predictors will be assessed according to the proportion and patterns of missingness. Model performance will be assessed using standard metrics including discrimination (C-statistic) and calibration (Hosmer-Lemeshow statistic), and internal validation will be performed with bootstrap resampling.

Bayesian networks allow a more flexible modelling approach, are more reliable when there are high correlations between predictor variables and allow a more efficient method to handle missing data, so an additional Bayesian network will be formulated using data from OUTLOOK. This model will consist of a target variable (mortality), multiple random variables (nodes), probabilistic dependencies between variables, and conditional probability tables that describe the direction and degree of influence between variables. The Bayesian model's performance will be assessed using the area under the curve-receiver operating characteristic (AUCROC), which is analogous to the C-statistic derived from the multivariate Cox proportional hazards model. Prediction models will be reported according to transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines (58).

Further data from TIMELY and Co-TIMELY including longitudinal changes in patient and caregiver quality of life, symptom burden, caregiver burden, and additional data from data linkage for end-of-life care characteristics, healthcare usage and costs will be analysed using a hierarchical modelling approach, which accounts for within- and between-patient variability for continuous outcomes, and Chi-square tests and logistic regression for categorical outcomes.

Sample size calculation

To guide sample size calculations in OUTLOOK, we estimated 40-50% 2-year mortality in patients who go on to dialysis and 60% for CKM patients (11). A minimum of 10 events per candidate variable is used as a benchmark for sample size calculations in model development studies. It is anticipated that 6-10 variables will be included in our final models based upon prior advanced CKD risk prediction models (59-62). However, larger sample sizes mitigate the risk of model overfitting, improve precision and performance of models, and enhance clinical utility (63). Accordingly, a sample size of 800 patients in OUTLOOK is targeted, with a target of 150 patients participating in TIMELY and 100 caregivers participating in Co-TIMELY.

Qualitative methodology

Caregivers in Co-TIMELY whose care-recipient is specifically receiving CKM will be asked to participate in a qualitative component. Minimum sample size is 20 caregivers and maximum sample size will be determined from data saturation, whereby no new themes are emerging from participant interviews. Single-encounter interviews will be conducted face-to-face or via teleconferencing for 30-60 minutes. These will be semi-structured using an interview guide, with participants asked to discuss their experiences of the planning of care, daily roles as a caregiver of a patient receiving CKM, and the impact being a caregiver has had on their life. Caregivers of patients who die during the study, who indicated on their consent that they are willing participate

in a post-death interview, will be approached no sooner than 3 months and no later than 6 months after their care-recipient's death to participate in a second semi-structured interview exploring end-of-life care. Target sample size for this end-of-life care component is 10 caregivers. Questions will be based on the Quality of Dying and Death (QoDD) tool (64, 65). Example interview questions include whether their care recipient was comfortable, how often end-of-life symptoms were controlled, whether they were at peace with dying, where they died, and what support was offered to the caregiver.

CONTEND is the final qualitative component of the program and involves single-encounter interviews with patients ≥70 years with kidney failure (eGFR ≤15mL/min/1.73m^2) and their caregivers. Eligible patients must have had a discussion about treatment pathways with their nephrologist and they are about to decide or have made a treatment decision within the last 2 years (ie. patients can be on dialysis or a CKM pathway initiated within 2 years). Patients and caregivers will be purposefully recruited during routine outpatient visits. The focus of CONTEND is upon shared decision-making, with a broad interview guide including questions on what information was provided to facilitate decision-making, experiences of the decision-making process, barriers/enablers of decision-making, and experiences of end-of-life care planning. This component aims for a minimum of 20 patients and 20 caregivers and maximum sample size determined from data saturation.

Transcripts from the Co-TIMELY qualitative component and from CONTEND will be thematically analysed using grounded theory, where data will be coded using NVivo software and abstract categories are constructed inductively to identify themes and relationships between themes. Data will be reported according to the consolidated criteria for reporting qualitative research (COREQ) (66).

Patient and public involvement statement

The design of this research program is shaped by prior literature on older patient priorities when making advanced CKD treatment decisions (4). The program began as pilot studies in 2017, with initial enrolment at 3 hospital sites. Informed by feedback from patients and caregivers, small changes to study design have been made to improve feasibility. The study design and participant information sheets for these studies will continue to receive regular feedback from the George Institute for Global Health Consumer Engagement Panel, consisting of patients with kidney disease and their caregivers.

ETHICS AND DISSEMINATION

Ethics approval for this study program has been obtained through the Sydney Local Health District Human Research Ethics Committee (2019/ETH07718, 2020/ETH02226, 2021/ETH01020, 2019/ETH07783). OUTLOOK is approved as a waiver of individual patient consent study in accordance with the 2018 National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (67). All other study components in this program involve direct patient contact and data collection beyond routine care, and accordingly involve written and informed consent. All study data is stored through a dedicated electronic data capture tool only accessible to site and central investigators. All data is managed confidentially and

anonymously, and will be stored for a minimum of 15 years in accordance with national guidelines (67). The results of this research are intended to be disseminated through peer-reviewed journals and presented at scientific meetings.

DISCUSSION

While there will always be some degree of prognostic uncertainty in patient care (68), the Elderly Advanced CKD Program aims to provide clinicians, patients and caregivers with accurate data and tools to reduce the extent of this uncertainty in the planning and provision of care for older patients with kidney failure. To our knowledge, this is the first study to prospectively follow an older kidney failure cohort to produce a risk prediction model for survival for use in the treatment decision-making phase. The nested work with patients and caregivers will provide detailed and longitudinal insights on important patient-reported outcomes such as quality of life and experienced burden of healthcare.

In the context of the exponential increase in elderly patients progressing to kidney failure in developed countries, this study program holds high clinical relevance. The program is currently enrolling across 6 sites in Australia, with the intention of further expansion to achieve national representation and enrolment targets for all studies by 2026. Baseline data from the 316 patients currently enrolled in OUTLOOK has found the following characteristics: mean age mean 83.5 years (range 75-95 years), predominantly community-dwelling (88%), and high prevalence of frailty (58%) and functional impairment (46% requiring a mobility aid). This is the population group in whom there is greatest equipoise regarding whether dialysis compared with CKM offers greater benefits. This work will thus generate valuable outcome data and ensure that the developed risk prediction tool will have direct clinical application. However, we acknowledge that such quantitative data alone will not overcome all challenges in complex decision-making. Accordingly, this research program incorporates qualitative work, to broaden the focus and encompass perspectives of patients and their families on treatment decision-making processes, experiences of CKM and end-of-life care.

Large multi-centre cohorts prospectively investigating outcomes in older patients with kidney failure are few. To date, there are two comparative studies. The European QUALity study (EQUAL) is an ongoing study recruiting patients ≥65 years with eGFR ≤20mL/min/1.73m^2 in 5 European countries, with prospective follow-up for 4 years (69). EQUAL aims to evaluate optimal timing of dialysis initiation among older patients, with additional insights regarding survival and longitudinal changes in patient-reported outcomes. Over 1500 of the targeted 3500 participants have been enrolled. The focus is on dialysis planning and the investigators have stated that patients on a CKM pathway will not be captured (70). The Canadian Frailty Observation and Interventions Trial (CanFIT) is a multi-centre observational cohort study which has enrolled 603 adult patients between 2012-2018 with eGFR <30mL/min who have had baseline frailty assessments and are being prospectively followed. CanFIT aims to examine the longitudinal trajectory of frailty and its associations with morbidity, mortality and patient-reported outcomes, but is capturing patients with less advanced kidney disease compared with those in the Australian Elderly Advanced CKD Program. Nonetheless, both EQUAL and

CanFIT complement the large-scale, robust and prospective aims of the OUTLOOK study. The collective aims of these studies, particularly those of the Elderly Advanced CKD Program, are to better inform discussions and decision-making processes for older patients with advanced kidney disease.

This work has limitations. Given the observational methodology, there is the potential for confounding from measured and unmeasured variables in the quantitative components of this program. While the study design aims to minimise the impact of lead-time and immortal time bias, complete elimination of these biases is not possible. Furthermore, while the study program aims to achieve multi-centre national representation, application of findings beyond Australia will have limitations.

Decision-making between treatment pathways is highly complex for older patients with kidney failure, their caregivers and clinicians. Challenges include accurate outcome predictions, communicating meaningful prognostic information, communicating associated uncertainty, and using this information to undertake systematic processes of shared decision-making and planning of care. The Elderly Advanced CKD Program is a large-scale multi-centre research program designed to address modifiable factors relating to each of these challenges by producing prospective, longitudinal, and robust data on survival, patient-reported outcomes and caregiver-reported outcomes, collected efficiently at a national level; to derive the necessary tools for patients, caregivers and clinicians; and, to understand patient and caregiver preferences for care. Such work is novel, practice-informing and much needed, as we face a growing population of elderly, frail and comorbid kidney failure patients.

CONTRIBUTORS

CF, MG, AS, NG and YM conceived the Elderly Advanced CKD Program and formulated protocols for study components. AS drafted the protocol manuscript, and NG, AM, CL, KY, YM, JR, GDT, CG, IA, SR, VN, CF and MG contributed to critical review and revisions of the manuscript.

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COMPETING INTERESTS

None declared.

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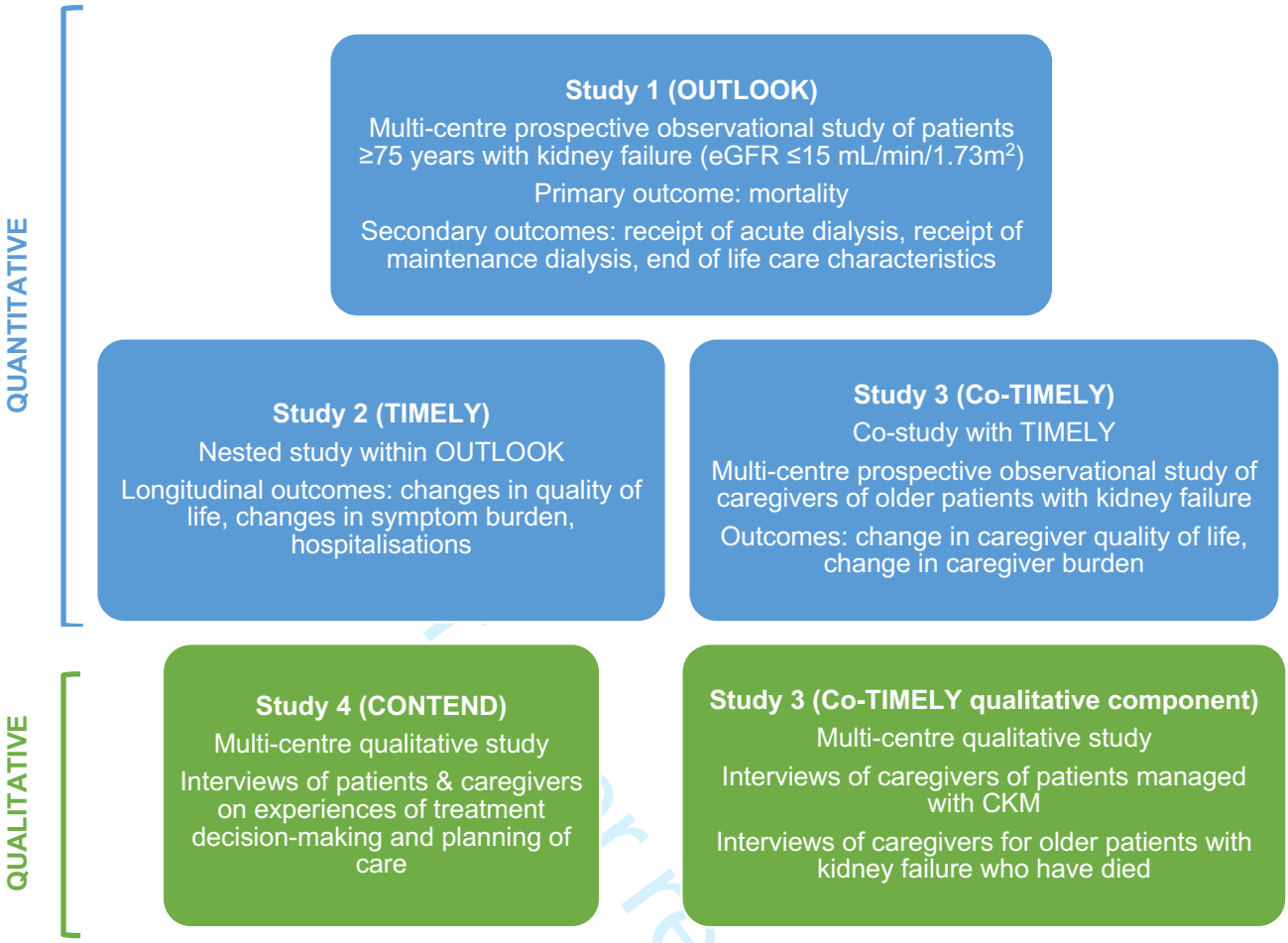
FIGURES

Figure 1. Components of the ELDERLY Program.

eGFR, estimated glomerular filtration rate; CKM, conservative kidney management; OUTLOOK, OUTcomes of Older patients with Kidney failure; TIMELY, Treatment modalities for the InfirM ElderLY with end stage kidney disease; Co-TIMELY, Caregivers of The InfirM ElderLY with end stage kidney disease; CONTEND, CONsumer views of Treatment options for Elderly patieNts with kiDney failure.



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Treatment decision-making and care among older adults with kidney failure: protocol for a multicentre, prospective observational cohort study with nested sub-studies and linked qualitative research (the Elderly Advanced CKD Program)

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Treatment decision-making and care among older adults with kidney failure: protocol for a multicentre, prospective observational cohort study with nested sub-studies and linked qualitative research (the Elderly Advanced CKD Program)

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ABSTRACT

Introduction: Shared treatment decision-making and planning of care are fundamental in advanced chronic kidney disease (CKD) management. There is limited data on several key outcomes for the elderly population including survival, quality-of-life, symptom burden, changes in physical functioning, and experienced burden of healthcare. Patients, caregivers and clinicians consequently face significant uncertainty when making life-impacting treatment decisions. The Elderly Advanced CKD Program includes quantitative and qualitative studies to better address challenges in treatment decision-making and planning of care among this increasingly prevalent elderly cohort.

Methods and analysis: The primary component is OUTLOOK, a multi-centre prospective observational cohort study that will enrol 800 patients ≥75 years with kidney failure (estimated glomerular filtration rate ≤15mL/min/1.73m^2) across a minimum of 6 sites in Australia. Patients entered are in the decision-making phase or have recently made a decision on preferred treatment (dialysis, conservative kidney management or undecided). Patients will be prospectively followed until death or a maximum of 4 years, with the primary outcome being survival. Secondary outcomes are receipt of short-term acute dialysis, receipt of long-term maintenance dialysis, changes in biochemistry, and end-of-life care characteristics. Data will be used to formulate a risk prediction tool applicable for use in the decision-making phase. The nested sub-studies TIMELY and Co-TIMELY will longitudinally assess quality-of-life, symptom burden, and caregiver burden among 150 patients and 100 caregivers, respectively. CONTEND is an additional qualitative study that will enrol a minimum of 20 patients and 20 caregivers to explore experiences of treatment decision-making and care.

Ethics and dissemination: Ethics approval was obtained through Sydney Local Health District Human Research Ethics Committee (2019/ETH07718, 2020/ETH02226, 2021/ETH01020, 2019/ETH07783). OUTLOOK is approved to have waiver of individual patient consent. TIMELY, Co-TIMELY and CONTEND participants will provide written informed consent. Final results will be disseminated through peer-reviewed journals and presented at scientific meetings.

Strengths and limitations of this study

- Prospective study design with multi-centre enrolment, broad representation and ease of data collection.
- Clinical outcome data collection to allow formulation of a risk prediction tool for use in the treatment decision-making phase.
- Nested sub-studies using a combination of quantitative and qualitative methodologies to provide wide-ranging assessment of important clinical outcomes for older patients with kidney failure, including survival, quality of life, symptom burden, receipt of dialysis, receipt of conservative kidney management, caregiver experiences, and end-of-life care.
- The study program is conducted across multiple sites in Australia and extrapolation of findings to other healthcare settings may not be applicable.

INTRODUCTION

Background

Chronic kidney disease (CKD) has risen from the 17th to the 12th leading cause of death globally over the last 25 years. Increasing numbers of individuals are progressing to the most advanced form of the disease, kidney failure (defined as an estimated glomerular filtration rate 15 mL/min/1.73 m^2 or lower) (1). For the increasing proportion of these patients with advanced age and multi-morbidity, complex decisions need to be made about treatment with kidney replacement therapy (KRT, with dialysis or kidney transplantation) or conservative kidney management (CKM). CKM involves a range of interventions to manage symptoms, improve quality of life, delay progression and manage complications, without the use of KRT.

In Australia, the prevalent dialysis population increased from 337 to 549 per million population between 2000 to 2019, with over half of prevalent patients aged ≥65 years and 26% aged ≥75 years (2). Whilst dialysis registries in many countries measure entry onto dialysis well, it is more challenging to quantify and understand the characteristics and outcomes of older patients with kidney failure who do not enter dialysis programs. A retrospective data linkage analysis combined deaths ascribed to kidney failure from the Australian National Death Index with the Australia and New Zealand Dialysis and Transplant Registry and identified 21,370 patients with death due to kidney failure over a 4-year period. Roughly half of the patients studied received dialysis (n=10,949) and a similar proportion died without ever receiving dialysis (n=10,421). The majority of the patients who did not receive dialysis were aged ≥75 years (3), the age group which also has the highest rate of incident dialysis in Australia and other developed countries.

For older patients with advanced CKD, the processes of decision-making between treatment pathways differ from that of younger patients, where there are clear differences in survival between treatment options. The greatest uncertainty occurs for patients aged 75 years or older, where few patients are medically suitable for transplantation, and there is limited data to inform decision-making, especially around the relative burden of dialysis and CKM and the outcomes they deliver for an older patient group. In turn, there are few tools to assist clinicians and patients in making decisions between these treatment pathways (4-9). Best practice approaches to decision-making should be timely, well-informed and individualised (10). Timely decisions are essential, as patients who commence dialysis in an unplanned manner have increased mortality (11, 12), reduced quality of life (13), and significantly higher healthcare costs (14). Ideally, an understanding of the various health outcomes important to older patients, including survival, quality of life, symptom burden, and experienced burden of healthcare should be at the centre of discussions (15-17). Furthermore, patients express a desire for frank, detailed prognostic information (18-20) but, in practice, there is little data to inform such prognostication. Real-world decision-making is thus challenging and highly variable.

Current knowledge of outcomes

Prospective clinical data collection is difficult in older patients, most notably seen in their under-representation in randomised clinical trials (21, 22). This reflects their high burden of comorbidities, frailty and cognitive impairment, and high experienced burden of treatment (23). Well-designed observational studies can achieve high inclusivity, external validity, and feasibility, and hold significant applicability for evaluating outcomes

among older advanced CKD patients. A scoping review of published observational literature reporting outcomes relevant to shared decision-making for older patients with kidney failure identified 248 publications, the majority from high-income English-speaking countries (USA, UK, Canada and Australia) and published in the last 10 years (6). However, 77% of studies exclusively pertained to dialysis patients (6), similar to that seen in reported meta-analyses (24, 25) and highlights the limited published literature on CKM (9).

A meta-analysis of patient survival among elderly patients with kidney failure from studies between 1976 to 2014 reported similar 1-year survival rates between dialysis and CKM (73.0-78.4% and 70.6%, respectively) (24). However, survival estimates for CKM patients were derived from only 12 of the total 89 studies and accounted for much fewer patients (724 vs. 294,196 for CKM and dialysis, respectively). There was also considerable residual heterogeneity for survival estimates within each treatment group, which may reflect changes in patterns of referral, acceptance onto dialysis programs and components of CKM provided by centres over the long period of the review. Other recent observational studies have been inconsistent, with some suggesting a survival advantage with dialysis compared to CKM (26, 27), and others suggesting limited or no survival advantage from dialysis in those patients with severe comorbidity, poor performance status or extreme age (28-30).

Many survival comparisons are also confounded by methodological issues (24, 31) such as; lead-time bias, immortal time bias, and indication bias. Lead-time bias arises from variability in defining a distinct starting point for CKM. This may result in a perceived survival advantage with CKM if survival time is calculated from an earlier starting point not equivalent to when dialysis would have been initiated. Conversely, immortal time bias occurs mainly in analysis of retrospective cohorts, when an index starting point is defined and patients go on to start dialysis much later (or not at all), giving rise to a perceived survival advantage ascribed to dialysis treatment. Indication bias is inherent to analysing survival in elderly kidney failure cohorts where there is expected referral of healthier patients for dialysis, and referral of older and frailer patients for CKM. Incorporating baseline covariates such as frailty and functional status into adjusted survival analyses aims to account for this, however such data is frequently not collected or available. These biases are magnified in retrospective analyses conducted after treatment decisions have been made, and notably 71 of the 89 included studies in Foote et al.'s systematic review were retrospective (24).

As identified in qualitative and discrete choice studies, a range of other outcomes are important to older patients, caregivers and clinicians in decision making, including quality of life, symptom burden, functional independence, experienced burden of healthcare and caregiver burden (32-35). Existing literature suggests that

the health-related quality of life of older patients on dialysis, compared to CKM, is broadly similar (36), that some older advanced CKD patients would 'trade-off' survival time in preference for maintaining functional independence (32-34), and that dialysis initiation is associated with high rates of deterioration of physical functioning among patients and high caregiver burden (37-39). Additionally, Canadian and UK studies suggest older dialysis patients spend significantly more time in hospital than CKM patients (26, 40). However, there are notable limitations to this data, as few studies have broad and systematic data collection, resulting in high risk of selection bias and limited adjustment for other variables (36). The majority of published studies are cross-sectional, and longitudinal data across either treatment pathway are lacking. Furthermore, patient outcomes, burden of healthcare and caregiver experiences are markedly dependent on healthcare structures. There is a need to assess these outcomes widely, including in the Australian context.

Program aims

In response to these limitations in data, we describe a program of work, the Elderly Advanced CKD Program, designed to explore decision-making and planning of care for older patients (defined in this program as age ≥75 years) with kidney failure. This includes addressing deficiencies in outcome data, broadening understanding of outcomes that are a priority to patients and caregivers, and applying this evidence to better support real-world decision-making processes. The aims of this study program are:

(a) To quantify survival in a cohort of older patients with kidney failure followed from estimated glomerular filtration rate (eGFR) ≤15mL/min/1.73m^2,

(b) To formulate a risk prediction tool for mortality applicable to patients at the time of treatment decision-making,

(c) To quantify other key patient outcomes among older patients with kidney failure in a prospective and longitudinal fashion, including quality of life, symptom burden, burden of planned and unplanned hospitalisations, and caregiver burden,

(d) To qualitatively explore patient and caregiver experiences of shared decision-making processes, planning of care, CKM and, ultimately, end-of-life care.

Table 1. Summary of the Elderly Advanced CKD Program components

	OUTLOOK	TIMELY	Co-TIMELY	Co-TIMELY (qualitative component)	CONTEND
Study type	Prospective observational cohort study	Prospective observational cohort study	Prospective observational cohort study	Qualitative study	Qualitative study
Target population for recruitment	Patients aged ≥75 years with kidney failure (eGFR ≤15 mL/min/1.73m^2)	Patients aged ≥75 years with kidney failure (eGFR ≤15 mL/min/1.73m^2)	Caregivers of patients enrolled in TIMELY	Caregivers of patients enrolled in TIMELY who are receiving CKM, caregivers of	Patients ≥70 years with kidney failure and their caregivers

				patients enrolled in TIMELY whose care-recipient has died	
Targeted sample size	800	150	100	20 caregivers of CKM patients, 10 caregivers whose care-recipient has died	20 patients, 20 caregivers
Primary outcome	Mortality	EQ-5D	EQ-5D	Caregiver experiences of CKM, caregiver experiences of end-of-life care for their care-recipient	Experiences of shared decision-making for kidney failure treatment
Secondary outcomes	Receipt of acute dialysis, receipt of long-term maintenance dialysis, end-of-life care characteristics	Satisfaction with life, symptom burden, living situation, hospitalisations	Satisfaction with life, caregiver responsibilities, caregiver burden	-	-
Frequency of follow-up	6 months	12 months	12 months	-	-
Study period	4 years	4 years	4 years	Single encounter interviews	Single encounter interviews

OUTLOOK, OUTcomes of Older patients with Kidney failure; TIMELY, Treatment modalities for the InfirM ElderLY with end stage kidney disease; Co-TIMELY, Caregivers of The InfirM ElderLY with end stage kidney disease; CONTEND, CONsumer views of Treatment options for Elderly patieNts with kiDney failure, eGFR, estimated glomerular filtration rate; CKM, conservative kidney management; EQ-5D, Euroqol-5 Dimension.

METHODS AND ANALYSIS

Program design

The program consists of 4 components (*Figure 1* and *Table 1*); a prospective observational cohort study with 3 components (including a small qualitative component), and a purely qualitative study examining patient and caregiver experiences:

1. OUTcomes Of Older patients with Kidney failure (OUTLOOK),
2. Treatment modalities for the InfirM ElderLY with end stage kidney disease (TIMELY),
3. Caregivers of The InfirM ElderLY with end stage kidney disease (Co-TIMELY), including a small qualitative component, and
4. CONsumer views of Treatment options for Elderly patieNts with kiDney failure (CONTEND).

Study design

OUTLOOK is a multi-centre prospective observational cohort study that aims to enrol 800 older patients with kidney failure (age ≥75 years and eGFR ≤15mL/min/1.73m^2) across a minimum of 6 sites in Australia. The study is ethically approved with a waiver of the need for individual patient consent. TIMELY is a nested cohort study that aims to enrol a subset of 150 patients within OUTLOOK, which requires individual patient consent for additional data collection relating to quality of life, symptom burden and functional status over time. The Co-TIMELY study aims to enrol 100 caregivers of older patients to prospectively examine caregiver responsibilities, quality of life and caregiver burden.

Study population and recruitment

Inclusion and exclusion criteria for OUTLOOK, TIMELY and Co-TIMELY are shown in *Table* 2. Patients are enrolled into OUTLOOK by study investigators if they meet the inclusion criteria, which are broad to minimise selection bias, maximise recruitment and increase external validity of the study. An eGFR ≤15mL/min/1.73m^2, as calculated by the Chronic Kidney Disease Epidemiology Collaboration formula, was chosen to define kidney failure, as it reflects a point at which patients and clinicians would be expected to be making decisions regarding planning for dialysis or CKM (4). This uniform definition provides an index date from which survival time will be determined for all participants, regardless of treatment pathway, aiming to mitigate lead-time bias and immortal time bias.

All patients enrolled into OUTLOOK will be screened for potential participation in TIMELY, with the only additional exclusion criteria for patient participation being extreme infirmity, significant cognitive impairment or insufficient English language skills (see *Table 2*), all of which would preclude participation in patient-reported outcome questionnaires. Potential TIMELY participants will be approached, and if willing to participate, will be asked to provide written informed consent. For the Co-TIMELY study, patients who consent to participate in TIMELY will be asked to nominate a primary caregiver. This caregiver will be screened against inclusion/exclusion criteria (see *Table 2*) and, if eligible, will be approached for participation with a view to provide written informed consent.

Table 2. Inclusion and exclusion criteria for OUTLOOK, TIMELY and Co-TIMELY

Inclusion criteria	Exclusion criteria
Patient age ≥ 75 years	Patient is receiving dialysis at the time of initial screening
Patient eGFR ≤ 15mL/min/1.73m^2	Patient not expected to survive 3 months beyond enrolment
Additional caregiver criteria for Co-TIMELY: - Nominated by the patient as a primary caregiver	Additional exclusion criteria for patients in TIMELY and for caregivers in Co-TIMELY: - Extreme infirmity (as assessed study team) - Significant cognitive impairment (inability to complete questionnaires as assessed by the treating nephrologist or study team, with a guiding lower threshold of ≤18 on mini-mental state examination) - English language skills insufficient to participate in questionnaires

eGFR, estimated glomerular filtration rate; OUTLOOK, OUTcomes Of Older patients with Kidney failure; TIMELY, Treatment modalities for the InfirM ElderLY with end stage kidney disease; Co-TIMELY, Caregivers of The InfirM ElderLY with end stage kidney disease.

Study period

Patients enrolled into OUTLOOK have baseline data collection and will be prospectively followed until death or for a maximum of 4 years, with follow-up occurring at 6-monthly intervals. Similarly, participants enrolled into TIMELY will be followed until death or for a maximum of 4 years, with follow-up questionnaires completed by participants at 12-monthly intervals. Caregivers enrolled into Co-TIMELY will be followed prospectively until either caregiver death, until 6 months after death of the corresponding care-recipient, or for a maximum of 4 years.

Measurement of baseline characteristics

Baseline data collection schedules for OUTLOOK, TIMELY and Co-TIMELY are shown in *Table* 3. OUTLOOK will only collect data from patient medical records and from healthcare providers involved in patient care (including from public/private hospitals, general practitioners, specialist records, and pathology providers). At enrolment, site investigators will review records and discuss with the treating team to determine the patient's planned treatment pathway (dialysis, CKM, or undecided) and the approximate timing of this decision.

Other baseline data collection incorporates wide-ranging measurement of patient characteristics that, based on prior literature, may influence the study's primary outcome of survival. These include patient demographics, medical history, medications, baseline pathology measurements, measures of functional status, and treatment plans. Baseline medical history will be used to derive a modified Charlson comorbidity score, a validated predictor of mortality in kidney failure patients, with a theoretical maximum score of 37 (41, 42). Baseline pathology measurements include serum creatinine, eGFR, albumin, haemoglobin, parathyroid hormone, and proteinuria (albumin:creatinine ratio or protein:creatinine ratio), all of which are markers of kidney disease progression (17). Measures of functional status are the Clinical Frailty Scale (43), Karnofsky performance score (44), and mobility status. The Clinical Frailty Scale is a 9-point scale that was chosen for its feasibility and its prior use in advanced CKD research showing an association with mortality (45). The Karnofsky functional performance score assesses functional status on a scale of 0 to 100, and it is the most widely used measure of functional impairment in chronic disease states including kidney failure (46). Additional treatment-related questions at baseline address the use of advance care planning, appointment of an enduring guardian, and the 'surprise question', which asks the treating nephrologist if they would be surprised if the patient died in the next 12 months and has demonstrated predictive ability for mortality in advanced CKD (47).

For TIMELY participants, two additional cognitive and nutritional baseline components will be collected during face-to-face visits. The mini-mental state examination (48) is a validated tool for assessment of cognition in the general population (49), and cognitive impairment (score of <24 out of a maximum score of 30) is associated with adverse health outcomes in advanced CKD (46). The subjective global assessment tool (50) assesses gastrointestinal symptoms, weight change, functional capacity and visual evaluation of subcutaneous tissue and muscle mass. It is the most commonly used nutritional assessment tool in Australian nephrology units, with higher rating scores associated with increased mortality in dialysis patients (51).

For caregivers participating in Co-TIMELY, baseline data includes caregiver demographics, caregiver characteristics (including relationship to the care-recipient and duration of caregiving), and caregiver responsibilities.

Table 3. Study schedule for data collection

	Timeline based on individual date of enrolment								
Data collection	**Baseline**	**6 mths**	**1 yr**	**18 mths**	**2 yrs**	**30 mths**	**3 yrs**	**42 mths**	**4 yrs**
Demographics (age, gender, ethnicity, primary language, marital status, residential status)	O								

Medical history (Charlson comorbidity score, medications)	O								
Functional status (Clinical Frailty Scale, Karnofsky Performance Score, mobility)	O								
Treatment pathway decision (dialysis, CKM, undecided), advance care planning status, surprise question	O								
Biochemistry	O	O	O	O	O	O	O	O	O
Survival status (including date, location and cause of death)		O	O	O	O	O	O	O	O
Receipt of dialysis		O	O	O	O	O	O	O	O
Cognitive assessment (MMSE)	T								
Nutritional status (SGA)	T								
Patient questionnaires: - Quality of life (EQ-5D, SWLS) - Symptom burden (iPOS-Renal)	T		T		T		T		T
Patient-reported changes in living situation, mobility and functional status	T		T		T		T		T
Patient-reported hospitalisations	T		T		T		T		T
Caregiver demographics (age, gender, ethnicity, primary language, education level)	C								
Caregiver characteristics (relationship to care recipient, duration of caregiving)	C								
Caregiver responsibilities	C		C		C		C		C
Caregiver questionnaires: - Quality of life (EQ-5D) - Caregiver burden (Zarit Burden Interview)	C		C		C		C		C
Data linkage (National Death Index, ANZDATA, Admitted Patient Data Collection, MBS, PBS)									O/T

'O' denotes data collection for both OUTLOOK & TIMELY, 'T' denotes data collection for TIMELY only, and 'C' denotes data collection for Co-TIMELY only. OUTLOOK, OUTcomes Of Older patients with Kidney failure; TIMELY, Treatment modalities for the InfirM ElderLY with end stage kidney disease; Co-TIMELY, Caregivers of The InfirM ElderLY with end stage kidney disease; CKM, conservative kidney management; MMSE, mini-mental state examination; SGA, subjective global assessment; EQ-5D, Euroqol-5 Dimension; SWLS, Satisfaction with Life Scale; ANZDATA, Australian and New Zealand Dialysis and Transplant Registry; MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Scheme.

Primary and secondary outcomes

The primary outcome of OUTLOOK is survival. Secondary outcomes are receipt of short-term acute dialysis, receipt of long-term maintenance dialysis, changes in biochemistry (including serum creatinine and eGFR), and characteristics of end-of-life care (including date, location, and primary cause of death).

In the nested sub-study TIMELY, additional outcomes are changes in health-related quality of life, changes in symptom burden, and patient-reported hospitalisations in the preceding 12 months. Health-related quality of life is assessed at baseline and in annual follow-up by the EuroQol-5 Dimension 3-Level (EQ-5D-3L) questionnaire and the Satisfaction with Life Scale (SWLS). The EQ-5D-3L is a generic quality of life measure assessing 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) (52). These responses can be compared against an Australian EQ-5D value set (53) to derive a single utility score ranging from less than 0 to 1 (with 0 representing death, negative values representing utilities worse than death and 1 representing perfect health). The SWLS is a 5-item scale with questions relating to ideal life, conditions of life, and satisfaction with present and past life (54). It has been used in various disease states including advanced CKD (36). Symptom burden is assessed with the Integrated Palliative Care Outcome Scale (iPOS-Renal), an inventory modified for use in advanced CKD populations (36, 55). It asks the responder about the impact of 15

kidney disease-specific physical symptoms and further emotional symptoms (each rated on a 5-point scale from 0, no impact, to 4, overwhelming impact) in the preceding week.

In the caregiver study Co-TIMELY, primary outcomes are changes in caregiver quality of life and changes in caregiver burden. Varied tools have been used to assess caregiver quality of life in prior CKD studies and the optimal tool is unclear (56). Baseline and annual caregiver quality of life is assessed in Co-TIMELY with the EQ-5D and SWLS as these are generic measures and they align with the TIMELY study. Caregiver burden is assessed at baseline and annual follow-up using the Zarit Burden Interview, a 12-question tool relating to feelings of personal strain from the caregiving role, with 5 responses for each question ranging from 0 (never) to 4 (almost always) (57). This tool is the most commonly used measure of subjective caregiver burden in advanced CKD studies (56).

Following study completion, study datasets will be linked to the National Death Index, Australian and New Zealand Dialysis and Transplant Registry (ANZDATA), Admitted Patient Data Collection (APDC), and Medicare and Pharmaceutical Benefits Schedules (MBS, PBS), using relevant national and state-based data linkage entities. Data linkage will be used to assess inpatient and non-inpatient healthcare usage and costs, dialysis characteristics and end-of-life care characteristics across treatment pathways.

Data analysis plan

From OUTLOOK, differences in survival between treatment groups will be analysed using Kaplan-Meier survival analysis and log-rank tests. A multivariable Cox proportional hazards model will be constructed using prespecified covariates based on clinical plausibility, including age, gender, comorbidity score, frailty score and functional performance score, with the aim of selecting a parsimonious model. Primary analyses will be a complete case analyses, however a multiple imputation approach for missing values of predictors will be assessed according to the proportion and patterns of missingness. Model performance will be assessed using standard metrics including discrimination (C-statistic) and calibration (Hosmer-Lemeshow statistic), and internal validation will be performed with bootstrap resampling.

Bayesian networks allow a more flexible modelling approach, are more reliable when there are high correlations between predictor variables and allow a more efficient method to handle missing data, so an additional Bayesian network will be formulated using data from OUTLOOK. This model will consist of a target variable (mortality), multiple random variables (nodes), probabilistic dependencies between variables, and conditional probability tables that describe the direction and degree of influence between variables. The Bayesian model's performance will be assessed using the area under the curve-receiver operating characteristic (AUCROC), which is analogous to the C-statistic derived from the multivariate Cox proportional hazards model. Prediction models will be reported according to transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines (58).

Further data from TIMELY and Co-TIMELY including longitudinal changes in patient and caregiver quality of life, symptom burden, caregiver burden, and additional data from data linkage for end-of-life care

characteristics, healthcare usage and costs will be analysed using a hierarchical modelling approach, which accounts for within- and between-patient variability for continuous outcomes, and Chi-square tests and logistic regression for categorical outcomes.

Sample size calculation

To guide sample size calculations in OUTLOOK, we estimated 40-50% 2-year mortality in patients who go on to dialysis and 60% for CKM patients (11). A minimum of 10 events per candidate variable is used as a benchmark for sample size calculations in model development studies. It is anticipated that 6-10 variables will be included in our final models based upon prior advanced CKD risk prediction models (59-62). However, larger sample sizes mitigate the risk of model overfitting, improve precision and performance of models, and enhance clinical utility (63). Accordingly, a sample size of 800 patients in OUTLOOK is targeted, with a target of 150 patients participating in TIMELY and 100 caregivers participating in Co-TIMELY.

Qualitative methodology

Caregivers in Co-TIMELY whose care-recipient is specifically receiving CKM will be asked to participate in a qualitative component. Minimum sample size is 20 caregivers and maximum sample size will be determined from data saturation, whereby no new themes are emerging from participant interviews. Single-encounter interviews will be conducted face-to-face or via teleconferencing for 30-60 minutes. These will be semi-structured using an interview guide, with participants asked to discuss their experiences of the planning of care, daily roles as a caregiver of a patient receiving CKM, and the impact being a caregiver has had on their life. Caregivers of patients who die during the study, who indicated on their consent that they are willing participate in a post-death interview, will be approached no sooner than 3 months and no later than 6 months after their care-recipient's death to participate in a second semi-structured interview exploring end-of-life care. Target sample size for this end-of-life care component is 10 caregivers. Questions will be based on the Quality of Dying and Death (QoDD) tool (64, 65). Example interview questions include whether their care recipient was comfortable, how often end-of-life symptoms were controlled, whether they were at peace with dying, where they died, and what support was offered to the caregiver.

CONTEND is the final qualitative component of the program and involves single-encounter interviews with patients ≥70 years with kidney failure (eGFR ≤15mL/min/1.73m^2) and their caregivers. Eligible patients must have had a discussion about treatment pathways with their nephrologist and they are about to decide or have made a treatment decision within the last 2 years (ie. patients can be on dialysis or a CKM pathway initiated within 2 years). Patients and caregivers will be purposefully recruited during routine outpatient visits. The focus of CONTEND is upon shared decision-making, with a broad interview guide including questions on what information was provided to facilitate decision-making, experiences of the decision-making process, barriers/enablers of decision-making, and experiences of end-of-life care planning. This component aims for a minimum of 20 patients and 20 caregivers and maximum sample size determined from data saturation.

Transcripts from the Co-TIMELY qualitative component and from CONTEND will be thematically analysed using grounded theory, where data will be coded using NVivo software and abstract categories are constructed

inductively to identify themes and relationships between themes. Data will be reported according to the consolidated criteria for reporting qualitative research (COREQ) (66).

Patient and public involvement

The design of this research program is shaped by prior literature on older patient priorities when making advanced CKD treatment decisions (4). The program began as pilot studies in 2017, with initial enrolment at 3 hospital sites. Informed by feedback from patients and caregivers, small changes to study design have been made to improve feasibility. The study design and participant information sheets for these studies will continue to receive regular feedback from the George Institute for Global Health Consumer Engagement Panel, consisting of patients with kidney disease and their caregivers.

ETHICS AND DISSEMINATION

Ethics approval for this study program has been obtained through the Sydney Local Health District Human Research Ethics Committee (2019/ETH07718, 2020/ETH02226, 2021/ETH01020, 2019/ETH07783). OUTLOOK is approved as a waiver of individual patient consent study in accordance with the 2018 National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (67). All other study components in this program involve direct patient contact and data collection beyond routine care, and accordingly involve written and informed consent. All study data is stored through a dedicated electronic data capture tool only accessible to site and central investigators. All data is managed confidentially and anonymously, and will be stored for a minimum of 15 years in accordance with national guidelines (67). The results of this research are intended to be disseminated through peer-reviewed journals and presented at scientific meetings.

DISCUSSION

While there will always be some degree of prognostic uncertainty in patient care (68), the Elderly Advanced CKD Program aims to provide clinicians, patients and caregivers with accurate data and tools to reduce the extent of this uncertainty in the planning and provision of care for older patients with kidney failure. To our knowledge, this is the first study to prospectively follow an older kidney failure cohort to produce a risk prediction model for survival for use in the treatment decision-making phase. The nested work with patients and caregivers will provide detailed and longitudinal insights on important patient-reported outcomes such as quality of life and experienced burden of healthcare.

In the context of the exponential increase in elderly patients progressing to kidney failure in developed countries, this study program holds high clinical relevance. The program is currently enrolling across 6 sites in Australia, with the intention of further expansion to achieve national representation and enrolment targets for all studies by 2026. Baseline data from the 316 patients currently enrolled in OUTLOOK has found the following characteristics: mean age mean 83.5 years (range 75-95 years), predominantly community-dwelling (88%), and high prevalence of frailty (58%) and functional impairment (46% requiring a mobility aid). This is the

population group in whom there is greatest equipoise regarding whether dialysis compared with CKM offers greater benefits. This work will thus generate valuable outcome data and ensure that the developed risk prediction tool will have direct clinical application. However, we acknowledge that such quantitative data alone will not overcome all challenges in complex decision-making. Accordingly, this research program incorporates qualitative work, to broaden the focus and encompass perspectives of patients and their families on treatment decision-making processes, experiences of CKM and end-of-life care.

Large, multi-centre cohorts prospectively investigating outcomes in older patients with kidney failure are few. To date, there are two comparative studies. The European QUALity study (EQUAL) is an ongoing study recruiting patients ≥65 years with eGFR ≤20mL/min/1.73m^2 in 5 European countries, with prospective follow-up for 4 years (69). EQUAL aims to evaluate optimal timing of dialysis initiation among older patients, with additional insights regarding survival and longitudinal changes in patient-reported outcomes. Over 1500 of the targeted 3500 participants have been enrolled. The focus is on dialysis planning and the investigators have stated that patients on a CKM pathway will not be captured (70). The Canadian Frailty Observation and Interventions Trial (CanFIT) is a multi-centre observational cohort study which has enrolled 603 adult patients between 2012-2018 with eGFR <30mL/min who have had baseline frailty assessments and are being prospectively followed. CanFIT aims to examine the longitudinal trajectory of frailty and its associations with morbidity, mortality and patient-reported outcomes, but is capturing patients with less advanced kidney disease compared with those in the Australian Elderly Advanced CKD Program. Nonetheless, both EQUAL and CanFIT complement the large-scale, robust and prospective aims of the OUTLOOK study. The collective aims of these studies, particularly those of the Elderly Advanced CKD Program, are to better inform discussions and decision-making processes for older patients with advanced kidney disease.

This work has some limitations. Given the observational methodology, there is the potential for confounding from measured and unmeasured variables in the quantitative components of this program. For example, socioeconomic status has not been objectively measured and may be a confounder in survival and quality of life analyses. While the study design aims to minimise the impact of lead-time, immortal time and indication bias, complete elimination of these biases is not possible. Furthermore, while the study program aims to achieve multi-centre national representation, application of findings beyond Australia will have limitations.

Decision-making between treatment pathways is highly complex for older patients with kidney failure, their caregivers and clinicians. Challenges include accurate outcome predictions, communicating meaningful prognostic information, communicating associated uncertainty, and using this information to undertake systematic processes of shared decision-making and planning of care. The Elderly Advanced CKD Program is a large-scale multi-centre research program designed to address modifiable factors relating to each of these challenges by producing prospective, longitudinal, and robust data on survival, patient-reported outcomes and caregiver-reported outcomes, collected efficiently at a national level; to derive the necessary tools for patients, caregivers and clinicians; and, to understand patient and caregiver preferences for care. Such work is novel, practice-informing and much needed, as we face a growing population of elderly, frail and comorbid kidney failure patients.

CONTRIBUTORS

CF, MG, AS, NG and YM conceived the Elderly Advanced CKD Program and formulated protocols for study components. AS drafted the protocol manuscript, and NG, AM, CL, KY, YM, JR, GDT, CG, IA, SR, VN, CF and MG contributed to critical review and revisions of the manuscript.

COLLABORATORS

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COMPETING INTERESTS

None declared.

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FIGURE TITLE AND LEGEND

Figure 1. Components of the Elderly Advanced CKD Program

eGFR, estimated glomerular filtration rate; CKM, conservative kidney management; OUTLOOK, OUTcomes of Older patients with Kidney failure; TIMELY, Treatment modalities for the InfirM ElderLY with end stage kidney disease; Co-TIMELY, Caregivers of The InfirM ElderLY with end stage kidney disease; CONTEND, CONsumer views of Treatment options for Elderly patieNts with kiDney failure.