Mixed-methods research in nephrology

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Running headline

Mixed-methods research in nephrology and kidney transplantation
Abstract

Mixed-methods research involves the mixing of at least one qualitative and one quantitative method in the same research project or set of related projects. Combined use of qualitative and quantitative research methods in nephrology has increased over the last 10 years. In this review we aim to advance understanding of mixed-methods research within the kidney community. Qualitative and quantitative techniques provide different but non-competing representations of what exists in the world: findings from qualitative research do not generalise to a large population, whilst those from quantitative research may not apply to individuals within the diverse and heterogenous larger population. Mixed-methods research combines these complementary representations, allowing the strengths of each method to be combined, and the strengths of one method to address the limitations of the other. Mixed-methods approaches can be used to i) gain a more complete understanding of a research problem, ii) explain initial results from one method with results from another, iii) generate instruments e.g. survey tools, interventions, iv) evaluate services, and v) optimize clinical trial design and delivery. There are three core mixed-methods designs: explanatory sequential, exploratory sequential, and convergent parallel, which can be combined. We discuss each design in turn before discussing analysis and integration of findings from the different methods. We provide case studies that illustrate the application of these study designs to kidney research questions. We briefly discuss mixed-methods systematic reviews and evidence synthesis before finally highlighting guidance on how to appraise published mixed-methods research.

Keywords

Mixed-methods; Qualitative; Quantitative; Kidney; Transplantation;
Introduction

Combined use of qualitative and quantitative research methods is increasing: the publication rate of ‘mixed-methods’ studies within nephrology has grown 10-fold in the last decade. In this review we aim to advance understanding of mixed-methods research within the kidney community. This review will help those involved in service evaluation and research to ascertain if the questions they face could best be answered with a mixed-methods approach, and whether evidence currently being generated by one approach could be enhanced by adding another method. It will also benefit those reading published reports of mixed-methods research, who must understand why the approach was taken, appraise whether it was appropriate, and appreciate the implications of any limitations.

We start by defining mixed-methods, before discussing the reasons for employing such an approach and outlining what is gained by combining qualitative and quantitative research. We then describe the common mixed-methods research study designs including when to use each and how to integrate findings, providing examples from kidney research. Finally we highlight guidance on how to appraise published mixed-methods work.

What is mixed-methods research?

Mixed-methods research involves ‘the mixing of at least one qualitative and one quantitative method in the same research project or set of related projects’\(^1\). The core characteristics of mixed-methods research are provided in Box 1\(^2\).
We undertook a search of MEDLINE on 21\textsuperscript{st} December 2021, from 1980 to present date, using the following free-text search: (("mixed-methods"[Title/Abstract] OR "mixed methods"[Title/Abstract] OR ("quantitative"[Title/Abstract] AND "qualitative"[Title/Abstract])) AND ("Renal"[Title/Abstract] OR "ki*ney*"[Title/Abstract])) AND (1980:2022[pdat]).

From 1709 screened results, 215 relevant articles were identified which reported mixed qualitative and quantitative research, 12 of which focussed on children. In 2011, just four mixed-methods kidney research papers were published, compared with 43 in 2021.

Mixing qualitative and quantitative research methods

The principles of qualitative and quantitative research approaches are summarised in Table 1. These reflect underlying research paradigms, particularly the ontological (what there is to know of the world)\textsuperscript{3} and epistemological (how one can acquire knowledge of it)\textsuperscript{4} standpoints. Qualitative and quantitative research provide different, non-competing, complementary representations of the same phenomenon\textsuperscript{5,6}.

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Box 1. Core characteristics of mixed-methods research (Creswell and Clark)

In mixed-methods, the researcher:

- Collects and analyses both qualitative and quantitative data rigorously in response to research questions and hypotheses,
- Integrates (or mixes or combines) the two forms of data and their results.
- Organizes these procedures into specific research designs that provide the logic and procedures for conducting the study, and
- Frames these procedures within theory and philosophy.
Table 1. Comparison of quantitative and qualitative research methods

<table>
<thead>
<tr>
<th></th>
<th>Quantitative research methods</th>
<th>Qualitative research methods⁶</th>
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</thead>
<tbody>
<tr>
<td>Questions</td>
<td>When? Where? What? e.g., What is the relationship between Kt/V and survival on peritoneal dialysis?</td>
<td>Why? How? e.g., Why did you choose peritoneal dialysis over haemodialysis?</td>
</tr>
<tr>
<td>Ontological standpoint – what exists and what is there to know?</td>
<td>Reality is objective and empirical: what is studied has an existence independent of the observer.</td>
<td>Reality is subjective: what is studied is socially constructed and personal.</td>
</tr>
<tr>
<td>Epistemological standpoint - how is knowledge acquired?</td>
<td>Positivist: knowledge is derived from objective observation of an external reality.</td>
<td>Interpretivist and constructivist: knowledge is developed from understanding a person’s view or experience of their constructed reality.</td>
</tr>
<tr>
<td>Method of reasoning</td>
<td>Deductive: hypotheses are generated from existing theory and tested through measurement of observable entities.</td>
<td>Inductive: theory and hypotheses are formulated as a result of the observations and findings.</td>
</tr>
<tr>
<td>Sampling</td>
<td>Population representative</td>
<td>Theoretical and purposive: often aiming for diversity and breadth</td>
</tr>
<tr>
<td>Sample</td>
<td>Large</td>
<td>Small</td>
</tr>
<tr>
<td>Data</td>
<td>Numbers</td>
<td>Non-numerical data e.g. words, pictures</td>
</tr>
<tr>
<td>Analysis</td>
<td>Quantification and statistical tests</td>
<td>Identification of patterns and themes</td>
</tr>
<tr>
<td>Data collection</td>
<td>Surveys, experiments using precise measurements from validated reliable instruments</td>
<td>Observations of peoples, cultures, and customs (ethnography), observations, focus groups, interviews</td>
</tr>
<tr>
<td>Strength of findings</td>
<td>Generalisability: findings should be applicable to a wider population</td>
<td>Deep and detailed findings may be applicable to specific individuals and contexts</td>
</tr>
<tr>
<td>Limitations</td>
<td>Findings at the population level may not apply to individuals, particularly those less represented in the sample. Risk of confirmation bias.</td>
<td>Findings may not apply to other people or other settings; they may be specific to the research participants.</td>
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</tbody>
</table>

⁶For further information and examples of the use of qualitative research in nephrology, we direct readers to the following referenced reviews⁷-¹⁰

Mixed-methods research combines these non-competing representations, and allows the limitations of one approach to be mitigated by the strengths of the other method. When the methods and, most importantly, the findings are integrated, mixed-methods approaches provides a greater insight into a problem than can any single method¹¹. For example, a team of researchers in the USA aimed to understand the outcomes and experiences of undocumented immigrants when they transitioned from emergency dialysis provision to regular scheduled treatment¹². The researchers employed a mixed-methods approach undertaking quantitative questionnaires and in-depth qualitative
interviews with individuals receiving dialysis before and after they moved from emergency to regular treatment. The quantitative questionnaire found that patients’ quality of life improved and symptom burden reduced after transition to regular dialysis, but, despite this, trust in their physicians and satisfaction with care were unchanged. The qualitative interview findings corroborated the quantitative findings and also provided deeper insight into why the levels of trust and satisfaction were unchanged. Participants described anxiety about navigating changes in care, including fear of the unknown, and anxiety about both tolerating additional dialysis sessions, and leaving the ‘safety net’ of their hospital for a remote dialysis provider. They also detailed an increased burden on family and employers, who needed to ensure regular transport was available, clarify insurance and cost implications, and minimise disruption to work\textsuperscript{12}. The quantitative study alone would not have identified the reasons for poor satisfaction despite improved health, and the qualitative study alone would not have captured the marked improvement in physical health. Using mixed-methods, not only are the strengths of each method combined, but the strengths of one method help to address the limitations of the other: mixed-methods are greater than the sum of their parts.

Mixed-methods primary research designs

Mixed-methods approaches can be used to i) gain a more complete understanding of a research problem, ii) explain initial results from one method with results from another, iii) generate instruments e.g. survey tools, interventions, iv) evaluate services, and v) optimize clinical trial design and delivery. Mixed-methods service development and evaluation studies generate an understanding of the service needs of a population by investigating both ‘what’ is needed (qualitative) and ‘how much’ (quantitative). Examples of questions in nephrology that could be best addressed with mixed-methods research are listed in Box 2.
Mixed-methods study designs may be planned from the start of a research programme (also described as ‘fixed’) or unplanned (also described as ‘emergent’). Unplanned approaches are commonly adopted when researchers encounter unforeseen issues with recruitment, retention or early data arise.

Quantitative and qualitative research methods can be combined in a plethora of novel and diverse designs. These vary in the methods used, the chronological order of the components applied, the relative importance given to each, and the degree of interaction and integration of their findings.

**Box 2. Examples of questions in nephrology and transplantation that could be best addressed with mixed-methods research**

- What explains geographical/ethnic/socioeconomic/gender inequality in access to kidney replacement therapy?
- What explains variation in COVID-19 vaccination rates between kidney units?
- What determines the prevalence of each kidney replacement therapy at a hospital site?
- What explains the difference in deceased-organ donation rates between different countries?
- How do patient preferences drive decisions between treatments for kidney replacement therapy?
- What outcomes matter most to patients following kidney transplantation?
- Are transplant recipients concordant with immunosuppression?
- How does advanced kidney disease affect quality of life/life participation?
- How well does a measurement tool e.g. the EQ-5D-5L, PHQ-9 perform amongst individuals with kidney failure? Assessment of validity and reliability.
- Is an intervention (e.g. to increase access to transplantation) feasible? Is an intervention acceptable and how does it effect change?
Many different ways of classifying research designs are discussed in the extensive mixed-methods literature. The various classifications arise from different specialisms including education\textsuperscript{13}, social sciences\textsuperscript{14}, and healthcare\textsuperscript{15,16}, and discuss different features of the design. Creswell and Clark are leaders in mixed-methods research with backgrounds in the field of Educational Psychology. They have described three core mixed-methods designs: explanatory sequential, exploratory sequential, and convergent\textsuperscript{2} (Figure 1. Core mixed-methods designs). Table 2 details when to use each of the different mixed-methods designs, and outlines the strengths and challenges of using each.

Explanatory sequential (Figure 1a)

This design comprises two distinct phases, starting with a quantitative study. The quantitative phase is followed by the collection of qualitative data that aims to explain or improve understanding of the findings of the initial quantitative study. The qualitative phase can be used to understand the quantitative findings in more depth, to understand data outliers, and to explain results that differ from previous research.

*Case study 1. Investigating knowledge and attitudes of Canadian First Nations people toward organ donation and transplantation: explanatory sequential design*

In Canada, organ donation and transplantation rates are low for aboriginal people despite a disproportionately high incidence of kidney failure compared with other ethnic groups\textsuperscript{17}. Davison and Jhangri used an explanatory sequential mixed-methods approach to understand knowledge of and attitudes toward organ donation and transplantation among First Nations people, and investigate how their beliefs influence decisions made about donation and transplantation\textsuperscript{17}. An initial quantitative phase comprised a 45-item survey which was completed by 198 participants. The subsequent qualitative phase purposively selected 21 individuals from survey respondents ensuring
diverse survey responses. In-depth semi-structured interviews were undertaken and analysed using a critical realist theoretical framework (Figure 2. Investigating knowledge and attitudes of Canadian First Nations people toward organ donation and transplantation: explanatory sequential design). The mixed-methods study found that whilst the majority (83%) of survey participants were in favour of transplantation, only 38% were willing to donate their organs after death and 44% had not considered it. Only 18.7% of survey respondents reported that traditional or cultural beliefs influenced their views on organ donation and transplantation. In qualitative interviews most participants raised the topic of traditional beliefs influencing their views, both for and against donation and transplantation. However, participants did not necessarily ascribe their beliefs to traditional values, instead, beliefs were considered ‘personal’ beliefs. Therefore, whilst the quantitative study didn’t find that traditional beliefs were an important barrier to donation and transplantation for most respondents, this may have reflected differences in understanding of the meaning of ‘traditional beliefs’ between researchers and respondents.

Exploratory sequential (Figure 1b)

In this design the first phase of work is a hypothesis generating and exploratory qualitative study. The subsequent quantitative phase involves the development of a quantitative tool using the qualitative findings. Examples include quantitative instruments and measures, discrete choice experiments (DCE), questionnaires, interventions for evaluation in a trial, and digital apps. The final phase involves quantitative evaluation of the developed tool before comparing the findings with the initial qualitative findings. This approach has been described as one of complementarity, in which elaboration, enhancement, illustration and clarification of the results of one methods are sought with the results from the other. Initial qualitative research can be used to identify important items to include in a quantitative measure, as well as the ‘real-life’ language with which these items should be described.
Exploratory sequential approaches have been employed to understand socioeconomic inequity in kidney transplantation in the UK, where socioeconomic deprivation is associated with a reduced likelihood of receiving a living-donor kidney transplant\textsuperscript{19}. To understand the reasons for this observed disparity, an exploratory sequential phase of research was combined with another quantitative study in a combined convergent design (Figure 3. Investigation of barriers to living-donor kidney transplantation: convergent design combined with an exploratory sequential phase). A qualitative study comprised in-depth interviews with people across socioeconomic strata who had not received a living-donor transplant to understand the reasons for this\textsuperscript{20}. Qualitative work suggested that: i) passivity, ii) disempowerment, iii) perceiving a lack of social support and iv) a short-term focus were important factors that prevented socioeconomically deprived individuals from accessing a living-donor kidney transplant\textsuperscript{20}. These themes were then further investigated quantitatively using a questionnaire that found them to explain a large proportion of the observed population-level inequity\textsuperscript{21}. A parallel quantitative multicenter prospective cohort study of potential living kidney donors found no strong evidence of a relationship between socioeconomic status and likelihood of donation having started assessment\textsuperscript{22}. Integration of findings from these studies allowed the researchers to determine that barriers to living-donor kidney transplantation existed early in donor identification rather than during donor assessment. This finding is vital for designing an intervention to reduce inequity in living-donor kidney transplantation, and ensuring it is delivered at the right time.

Exploratory sequential analyses are often used to develop and use quantitative instruments such as Patient Reported Outcome or Experience Measures (PROMs and PREMs)\textsuperscript{23}. The Home Dialysis Care Experience instrument was designed to measure the experience of patients undergoing home dialysis. Development involved qualitative focus groups and interviews with a mixed-stakeholder group comprising people on home dialysis, home dialysis nurses, patient care partners and nephrologists\textsuperscript{23}. Through this a list of items for possible inclusion in the instrument was generated.
The relative importance of these was then evaluated in a quantitative prioritization study. The drafted Home Dialysis Care Experience instrument was then qualitatively evaluated with cognitive interviews to evaluate item interpretability, order and structure, and the instrument refined in light of findings\(^23\).

Convergent (Figure 1c)

Convergent parallel designs implement concurrent but independent quantitative and qualitative strands, the results of which are then integrated during interpretation. This design aims to generate a more complete understanding of a problem under investigation, to validate one set of findings with the other, or determine if participants respond in similar ways to open-ended qualitative questions and quantitative survey measures\(^2\).

A convergent mixed-methods approach is being employed to investigate the palliative care needs, health-related quality of life, and survival of people with kidney failure in Uganda\(^24\). In this mixed-methods longitudinal study qualitative and quantitative data will be collected concurrently. Health-related quality of life scores of people receiving haemodialysis will be compared to scores of people receiving conservative management, and factors associated with quality of life investigated. It will also investigate survival of the two patient groups. The qualitative research will investigate the lived experience of the participants, and the mixed-methods analysis will investigate how this compares to the quantitative quality of life and survival measures\(^24\).
### Table 2. Choosing a mixed-methods research design

<table>
<thead>
<tr>
<th>Intent</th>
<th>Exploratory sequential</th>
<th>Exploratory sequential</th>
<th>Convergent</th>
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<tbody>
<tr>
<td>To explain findings from an initial quantitative phase using a successive qualitative approach</td>
<td>To use findings from a qualitative phase of research to inform the design of a subsequent quantitative phase (e.g., measurement tool, survey, intervention, app)</td>
<td>To obtain and integrate complementary quantitative and qualitative data on the same one topic</td>
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<table>
<thead>
<tr>
<th>When to use</th>
<th>Employ this approach when:</th>
<th>Employ this approach when:</th>
<th>Employ this approach when:</th>
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<tbody>
<tr>
<td></td>
<td>Time and funding permit a sequential design</td>
<td>Time and funding permit a sequential design</td>
<td>Time is limited</td>
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<td></td>
<td>The research team does not have capacity to undertake two phases of research in parallel.</td>
<td>The research team does not have capacity to undertake two phases of research in parallel.</td>
<td>The participants for the quantitative and qualitative phases are the same: it is more efficient and less burdensome than sequential research.</td>
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<td></td>
<td>Previous research exists to inform the design of the initial quantitative phase (e.g., variables important to the research question and associated quantitative measurement tools may exist.)</td>
<td>The important variables to measure are not yet known.</td>
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<td></td>
<td>Quantitative measures/instruments/interventions are unavailable or require adaptation for use in a new population.</td>
<td>The researcher wants to assess the generalizability of qualitative findings.</td>
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<td></td>
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<tr>
<td>Integration</td>
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<td></td>
<td>The focus of the explanatory qualitative phase is determined by the quantitative findings.</td>
<td>The findings from the exploratory qualitative phase are used to design the subsequent quantitative work.</td>
<td>The two strands have a parallel focus on aspects of the same question</td>
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<td></td>
<td>The phases are integrated through explanation and enlightenment of the quantitative data, using the qualitative findings.</td>
<td>The phases are integrated by grounding the developed tool or intervention in the experiences, perspectives, views, and culture of the participants.</td>
<td>The phases are integrated on completion, often using concurrent display (for example a joint display table or graphical joint display), or in the text by presenting quantitative and qualitative findings together.</td>
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<td></td>
<td>Following the quantitative phase the researcher describes how the quantitative findings build on the earlier qualitative work.</td>
<td>Transformation of variables e.g., counts of code frequency</td>
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<td>Strengths</td>
<td>Challenges</td>
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<tr>
<td>• Single researchers with limited team capacity can undertake this work.</td>
<td>• Time</td>
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<tr>
<td>• May be easier to prepare reports for publication, as a single paper can</td>
<td>• The design of the qualitative phase cannot be fully described until</td>
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<td>have clear quantitative and qualitative sections, or the work can be</td>
<td>completion of the qualitative phase: this can lead to problems acquiring</td>
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<td>published in two separate but related papers.</td>
<td>funding for both phases at the outset.</td>
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<td>• The addition of a qualitative phase to a quantitative study can make</td>
<td>• Participant burden if participants for the qualitative phase are selected</td>
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<tr>
<td>qualitative research more accessible to primarily quantitative</td>
<td>from the quantitative phase.</td>
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<td>researchers.</td>
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<td>researchers.</td>
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<tr>
<td>• Efficient</td>
<td>• Merging findings, particularly if contradictory or divergent. May</td>
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<tr>
<td>• Minimises burden on participants</td>
<td>require prioritization of one method above another, or further research.</td>
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<td>• Phases can be undertaken by independent researchers with particular</td>
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<td>expertise.</td>
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Combining designs

The described research designs are often combined in larger programmes of mixed-methods research. An example is the combination of a convergent and sequential analyses in determining patient and other stakeholder treatment preferences in DCEs. DCEs are research tools used to provide quantitative information regarding individuals’ preferences. In health research they are often used to quantify patients’ preferences for different attributes (characteristics) of treatments and the trade-offs they are willing to make between them. Real-world decisions are closely simulated through the simultaneous consideration of treatment characteristics. DCEs have been used to measure the preferences of patients with chronic kidney disease considering organ donation and allocation, and end-of-life care. Where the attributes that are important to people making healthcare decisions are unknown or incompletely described, those used in a novel DCE are best determined by preceding qualitative and quantitative research.

Case study 2: Understanding decision-making regarding kidney replacement therapy

Morton et al. used a 4 stage mixed-methods approach to investigate the most important characteristics of dialysis to patients in Australia, including the trade-offs they were willing to make in choosing between dialysis and conservative care (Figure 4. Understanding decision-making regarding kidney replacement therapy: combining convergent and explanatory sequential designs). Firstly they conducted a systematic review and thematic synthesis of 18 qualitative research that had investigated the views of patients and carers in treatment decision making for chronic kidney disease. Four major themes were identified as being central to treatment decision making: confronting mortality, lack of choice, gaining knowledge of options, and weighing alternatives.

In addition a qualitative interview study was undertaken: this comprised semi-structured interviews with 95 Australian dialysis and transplant patients to investigate how they perceived treatment
options. Freedom, convenience, self-care, effectiveness, and simplicity were commonly cited positive treatment characteristics. Confinement, risk, family burden, pain, and time commitment were negative characteristics associated with treatment.

Thirdly, they employed a mixed-methods nominal group technique to obtain individual and group rankings of dialysis characteristics. Nominal group technique uses highly-structured focus groups to gather information from relevant participants about a given issue. It consists of several steps in which participants rank, discuss and then re-rank a series of items. Patient groups agreed that the most important characteristics were i) survival, ii) convenience of dialysis at home, and iii) dialysis-free days. Transcripts of these focus groups were analysed qualitatively to explore the rationale for ranking. This revealed that maximizing survival was considered a ‘given’, that was not felt to require ranking. It also revealed that dialysis was considered a ‘holding measure’ extending survival until a cure was found or transplantation occurred, but not all dialysis modalities were considered worth living for.

The findings from the systematic review, qualitative interviews and ranking exercise were then used to inform the selection of characteristics and levels for a DCE. This study investigated the influence of specific treatment characteristics (life expectancy, number of visits to the hospital per week, ability to travel, time spent undergoing dialysis, time of day at which treatment occurred, availability of subsidized transport and flexibility of the treatment schedule) on patients’ preferences for dialysis versus conservative care. 105 adults with advanced kidney disease completed a DCE survey. Patients were willing to forgo 7 months of life expectancy to reduce the number of required visits to hospital and 15 months of life expectancy to increase their ability to travel.

Mixed-methods research in trial designs

Qualitative research can be embedded in a quantitative experimental clinical trial, to enhance acceptability of an intervention before evaluation, optimize recruitment, understand the
experience and impact of the intervention and trial participation on individuals\textsuperscript{36}, and to assess feasibility of intervention delivery and trial evaluation\textsuperscript{33,36}.

**Intervention development**

The ASK: improving AcceSs to living-donor Kidney transplantation study in the UK, funded by the Wellcome Trust, is a mixed-methods trial. In the ASK programme of research an initial qualitative phase of in-depth interviews with diverse stakeholders was undertaken to develop a multicomponent complex intervention for trial\textsuperscript{33}. Potential components and study resources were discussed with patients, family members and healthcare professionals to optimize acceptability and engagement, and assess feasibility prior to evaluation in a trial. Following qualitative development, the feasibility of delivery, implementation, mechanisms of impact, effectiveness and cost-effectiveness are under evaluation in a quantitative clinical trial with a parallel process evaluation\textsuperscript{37}.

**Recruitment optimisation**

The Qualitative Research Integrated within Trials (QuinteT) team led by Professor Jenny Donovan in the UK developed the QuinteT Recruitment Intervention (QRI)\textsuperscript{34,35}. The aim of the QRI is to understand and optimize the process of recruitment to Randomised Controlled Trials (RCTs) as it occurs, to gather evidence about the origin of difficulties quickly, and then to produce a plan to address the difficulties\textsuperscript{34}. The QRI can be applied in the feasibility/pilot stage, or to an RCT that has encountered recruitment challenges. The QRI was developed for the ProtecT (Prostate Testing for Cancer and Treatment) trial\textsuperscript{38}. ProtecT was designed to evaluate the effectiveness of three treatments for prostate cancer (active monitoring, radical prostatectomy and radical radiotherapy). When the trial experienced difficulties recruiting, a qualitative research study revealed that recruiters had difficulty discussing equipoise and presenting treatments equally, using terminology that was misinterpreted by participants\textsuperscript{38}. Changes to the order of presenting treatments encouraged emphasis on equivalence: the non-radical arm was renamed, from ‘conservative monitoring’ or ‘watchful waiting’ to ‘active monitoring, and recruiters were provided with guidance
on how to present clinical equipoise more convincingly. Following these changes the randomization rate in the ProtecT study increased from 40% to 70%.

Case study 3: The Prepare for Kidney Care trial

The Prepare for Kidney Care trial has been designed to compare preparation for dialysis versus preparation for conservative care in older adults with stage 5 kidney disease. Qualitative phases of work have been embedded alongside the quantitative clinical trial (Figure 5. Flow diagram for the Prepare for Kidney Care study: mixed-methods research to optimize clinical trials.). Prior to commencement of the trial, interviews with healthcare professionals were conducted to explore attitudes to the trial and potential barriers and facilitators. The QRI has been embedded in Prepare for Kidney Care to identify sources of recruitment difficulties, and implement interventions to address these by a) mapping patient eligibility and recruitment pathways b) audio recording and observation of recruitment appointments c) semi-structured interviews d) observation of trial management group and investigator meetings, e) analysis of screening logs, and f) document analysis of trial materials. Finally qualitative methods are being used to explore the acceptability of the intervention and trial processes, and to understand reasons for non-compliance/protocol deviations.

Analysis and interpretation

Integration of qualitative and quantitative findings is crucial in the analysis and reporting of mixed-methods research. How findings are integrated is determined by the questions being investigated, the study design and the intent of integration. In an explanatory sequential design, integration happens by using qualitative research to explain and expand on the preceding quantitative phase of work. A statistical analysis of the quantitative data is undertaken, and the results that need further explanation are identified. Purposeful qualitative sampling is then in part driven by the statistical
results: the aim is to identify a qualitative sample and questioning approach that will best explain the quantitative results. The findings of the qualitative analysis are then used to answer the questions arising from the qualitative phase.

In an exploratory sequential study, the qualitative findings are used to design a subsequent quantitative feature (e.g., a new instrument). How the qualitative findings have influenced design of the quantitative feature should be made explicit in narrative text or a diagram. The quantitative instrument should be piloted and refined, often with further qualitative research to evaluate features such as the acceptability, engagement, face validity, and reach of the developed instrument. The developed quantitative instrument can then be used in a large sample, and the findings from this definitive quantitative evaluation compared with the initial qualitative findings.

In a convergent design, the aim is to gain a comprehensive, rich, and complete understanding of a problem. The qualitative and quantitative research strands are analysed separately, and then findings are compared for commonalities and conflicts. The findings are then examined for how they expand and add depth to each other, and to explore how generalizable qualitative findings may be. Side-by-side comparisons of quantitative and qualitative results for a single item/question are often presented. Triangulation can be used to assess whether the findings from each method agree (converge), offer corresponding information (complement), or contradict each other (discrepancy, dissonance or disagreement). Sometimes data is transformed (e.g. qualitative data is quantified by counting the number of times a code appears in the data, or by counting the presence (1) or absence (0) of a specific theme in each participant’s data) in order to combine findings. It is more common in mixed-methods research to transform qualitative data into numerical counts that the reverse. This approach can be considered reductive, with erosion of the depth of information generated through qualitative research. Some researchers use a ‘mixed-methods matrix’ to integrate qualitative and quantitative data collected from individual participants. Here, the data collected on a participant can be examined in detail—for example, an individual’s response to a quantitative questionnaire can be
compared to a transcript of their qualitative interview. This can be displayed in a matrix in which each row represents a single participant for whom there is both qualitative and quantitative data, and the columns display different data collected on each participant\textsuperscript{41}.

In convergent study analysis, the items on which there is convergence are often listed before the items on which there is divergence or disagreement. When findings from the qualitative and quantitative methods are disconfirming, further investigation and research is required to understand the reasons for this, by investigating factors such as context, methodological problems or errors, sources of bias, sample differences, face validity of research questions to participants. Following interrogation of the qualitative and quantitative research methodologies used the researcher may identify that one has been undertaken more robustly or is more reliable, and thus identify those findings as more trustworthy. However, the conclusion may be that more research is required to resolve the discrepancies\textsuperscript{2}.

Findings from quantitative and qualitative work can be published sequentially or integrated as a single work. Barriers to publication of qualitative work in the medical literature are well-described\textsuperscript{43}. These can lead to insufficient reporting of qualitative components from mixed-methods work, making judgement of quality and rigor impossible\textsuperscript{44}. The tendency for inadequate reporting of qualitative components can be countered through the adoption of reporting guidelines\textsuperscript{44,45} and with separate in-depth publication of qualitative components including clear description of analysis and integration (see ‘Evaluating published mixed-methods research’).

Mixed-methods systematic reviews

A mixed-methods systematic review applies the principles of mixed-methods research to the review process: qualitative and quantitative studies focused on the same topic are combined to generate evidence to guide decision-making. By including diverse forms of evidence from different types of research, mixed-methods reviews try to maximize the findings and the
ability of the findings to inform policy and practice. True mixed-methods evidence syntheses should attempt to combine and integrate the findings from studies of each method, rather than simply presenting separate syntheses for each method, with a ‘brief narrative discussion of the ‘total’ results. The field of mixed-methods systematic reviews is still emergent and whilst there is a growing literature on reviews that include both quantitative and qualitative data synthesis, most fail to unite them in a ‘final’ synthesis.

The approach to a mixed-methods systematic review can be ‘sequential’, in which the syntheses occurs consecutively, or ‘convergent’, in which the syntheses occurs simultaneously. In a sequential approach the findings from one study type e.g., qualitative are synthesized, and the results are used to generate a question, which the second synthesis is designed to address. The results of the second synthesis could generate a third question and so on.

The convergent approach can be further divided into ‘segregated’ and ‘integrated’. In a segregated approach, qualitative and quantitative evidence are synthesized separately, then the findings compared to determine if they confirm, refute, or complement each other. Integrated approaches combine both types of data into a single synthesis, requiring transformation of one data type into another as described above. Either quantitative data must be converted into themes, codified and then presented along with qualitative data in a meta-aggregation, or qualitative data must be converted into numerical format and included with quantitative data in a statistical analysis.

Case study 4: Experiences of caring for people receiving dialysis

A mixed-methods systematic review investigated the perspectives and experiences of family members and friends who provide support for adults receiving dialysis therapy. A segregated
approach was taken in which quantitative (13 studies) and qualitative (7 studies) evidence were synthesized separately before being combined in an overarching synthesis. The quantitative findings highlighted the burden associated with caregiving and the negative impacts (depression and anxiety, lower quality of life and poorer sleep quality). The findings from the qualitative synthesis corroborated these findings. However, whilst the quantitative synthesis found that informal caregivers indicated receiving a high level of social support on quantitative measures, the qualitative synthesis found that caregivers still reported experiencing social isolation. In addition, whilst the quantitative synthesis largely identified only negative impacts, a unique finding from the qualitative synthesis was that caregivers also reported personal growth (gaining confidence and inner strength). This positive outcome would not have been identified by the quantitative synthesis alone.

Evaluating published mixed-methods research

To evaluate the quality of a mixed-methods study, the quality and appropriateness of the qualitative and quantitative components must be assessed, as should the integration of both methods. Several reporting guidelines exist for qualitative research and quantitative methods. The Enhancing the QUAlity and Transparency Of health Research (EQUATOR) network identifies 10 reporting guidelines for mixed-methods studies. Three reporting guidelines provide general guidance. This includes the Good Reporting of A Mixed Methods Study (GRAMMS) guidelines (Box 3). The GRAMMS guidelines were developed following a review of 75 reports from mixed-methods studies funded by the Department of Health in England, UK. This found that overall, there was a lack of transparency in the reporting of mixed-methods studies in health services research. The mixed-methods design was largely ignored, and only the separate components of a study were described. Integration of findings from each method was rarely undertaken. Other guidance on reporting mixed-methods research largely refers to specific study designs: this includes guidance for Realist
evaluations (RAMESES-II)\textsuperscript{57}, for Evaluating complex interventions in end of life care (MORECare)\textsuperscript{58} and the Standards for Reporting Implementation Studies (STaRI) statement\textsuperscript{59}. Guidance for the publication and appraisal of mixed-methods research in the development of quantitative preference study protocols and survey instruments is also available\textsuperscript{44}. 

**Box 3. Good Reporting of A Mixed Methods Study (GRAMMS)**

1. Describe the justification for using a mixed methods approach to the research question
2. Describe the design in terms of the purpose, priority and sequence of methods
3. Describe each method in terms of sampling, data collection and analysis
4. Describe where integration has occurred, how it has occurred and who has participated in it
5. Describe any limitation of one method associated with the present of the other method
6. Describe any insights gained from mixing or integrating methods

**Conclusion**

Mixed-methods research allows the strengths of qualitative and quantitative methods to be combined, to gain a more complete understanding of a research problem, generate instruments and optimize clinical trial design and delivery. We have provided guidance on study design and analysis for those considering undertaking mixed-methods projects, and for those reading and appraising published research using this increasingly popular approach.
References


54. Enhancing the QUALITY and Transparency Of health Research (EQUATOR) network Available at: https://www.equator-network.org/ [Accessed 23rd December 2021].


Figures

Figure 1. Core mixed-methods designs

Figure 2. Investigating knowledge and attitudes of Canadian First Nations people toward organ donation and transplantation: explanatory sequential design

Figure 3: Investigation of barriers to living-donor kidney transplantation: convergent design combined with an exploratory sequential phase

Figure 4. Understanding decision-making regarding kidney replacement therapy: combining convergent and explanatory sequential designs

Figure 5. Flow diagram for the Prepare for Kidney Care study: mixed-methods research to optimize clinical trials.
Quantitative data collection and analysis

Qualitative study driven by findings from the quantitative phase

Interpretation and integration - using qualitative findings to explain and expand on the quantitative work

Qualitative data collection and analysis

Quantitative instrument development using qualitative findings e.g., survey measure, intervention, App

Interpretation of quantitative findings in light of initial qualitative study

Further rounds of application and testing with embedded qualitative methods

Quantitative data collection and analysis

Qualitative data collection and analysis

Analysis of quantitative data

Interpretation and integration through comparing and contrasting, triangulation and transformation

Analysis of qualitative data
Quantitative data collection and analysis
45-item survey investigating knowledge and attitudes about organ donation and transplantation
198 participants

Qualitative study driven by findings from the quantitative phase

Qualitative data collection and analysis
In-depth semi-structured interviews investigating knowledge and attitudes about organ donation and transplantation
21/198 survey participants

Interpretation and integration: identification of barriers to donation and transplantation in First Nations in Canada
Qualitative Interview Study
Interviews with transplant recipients to understand reasons for not receiving a living-donor transplant

Quantitative study developed to explore whether themes explain observed population inequity

Quantitative Questionnaire Study
Case-control study comparing living-donor transplant recipients with deceased-donor recipients

Integration and interpretation
Results merged and compared: barriers to living-donor kidney transplants identified

Quantitative analysis
Prospective cohort study of potential living kidney donors in the UK
18 qualitative studies investigating view of patients and carers in kidney disease treatment decision making

Semi-structured interviews with 95 people receiving dialysis or living with a transplant
Audio-recording of interviews
Transcription
Coding and analysis of transcripts

Interpretation and integration: important characteristics of kidney replacement therapy identified attributes for Discrete Choice Experiment

Quantitative research

Mixed-methods nominal group technique study

Qualitative systematic review and thematic synthesis

Qualitative interview study

6 ‘nominal group’ focus groups
Audio-recording of ranking discussions
Transcription
Coding and analysis of transcripts

Quantitative research

6 ‘nominal group’ focus groups
Individual generation of important dialysis characteristics
Group discussion
Characteristics added from previous groups and literature
Individual re-ranking of characteristics
Group discussion and group ranking

Discrete Choice Experiment

Rating and ranking of kidney treatment characteristics of importance
Trade-offs determined
Assessed for eligibility
All patients aged 65+ with stage 5 Chronic Kidney Disease

Eligible
Randomised

Prepare for responsive management (n=256)
1. Assess and launch
   Home visits
   Liaise with MDT
   Prepare for responsive management

2. Responsive management
   Routine support
   - Review in renal out-patients
   - Monthly telephone contact
   - One home visit by renal HCP per year
   - Communication with MDT
   Responsive support
   - In renal out-patients
   - In the community (telephone calls, home visits, emergency surgery appointments)

3. Supportive care
   Home visits
   Communication with MDT

Prepare for dialysis (n=256)
1. Assess
   Clinic visits
   Liaise with MDT
   Prepare for renal dialysis

2. Renal dialysis
   Clinic visits
   Renal dialysis according to local protocols
   Communication with MDT

3. Supportive care
   Home visits
   Communication with MDT

Follow up