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The development of the Australian national Palliative Care Clinical Studies Collaborative 'Integrating Qualitative Research into Clinical Trials Framework'

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Abstract

Qualitative methodologies ~~may~~ have multiple contributions to health research, including improving baseline understanding in new areas of enquiry; questioning existing assumptions; understanding viewpoints of specific sub-groups; and offering complex, contextual information.

While the role of qualitative research within mixed methods approaches is well documented, the contribution to clinical trial design and conduct is less well recognized.

The Australian Palliative Care Clinical Studies Collaborative and Cancer Symptom Trials have developed a framework to detail how qualitative research might contribute to each key aspect of clinical trials. This practical framework provides real world examples including sample qualitative questions to consider at each phase of controlled clinical trial development.

As the number of randomised clinical trials in palliative care increases, a readily accessible approach to integrating qualitative research into clinical trial design and conduct is needed so that its full potential for improving study recruitment, conduct, outcomes, interpretation and implementation may be realised.

Key words: *qualitative research, mixed methods, randomised clinical trials, trial development*

Background

Qualitative research is rightly recognised as having value and legitimacy in health research (1-4). Qualitative approaches may serve multiple roles in health research, including: providing insights into areas of enquiry where there is little baseline understanding; questioning existing assumptions in health care; understanding the viewpoints of specific sub-groups and providing understanding that is contextual and complex. Used as a means to explore ideas, perceptions, experiences and other latent phenomena in rich detail, and to build an understanding of range and depth, qualitative research not only serves to answer many research questions, but may also act to generate hypotheses (5).

In palliative care, qualitative approaches have an important role because there are many phenomena that are poorly understood (for example, experiences of loneliness at the end of life), or that may not be readily measurable or understood using an objective instrument (for example, changes in the nature of relationships in serious illness) (6, 7). When conducted rigorously, qualitative methods, like quantitative methods, offer valuable approaches for wide application across palliative care research. Whether a quantitative or qualitative approach is needed – or whether these should be combined within a mixed methods approach – should be determined by the nature of the research questions (3).

Because palliative care is focused on improving patient perceptions of their symptoms, functioning independently for as long as possible and quality of life rather than more objective outcomes such as survival, clinical trials in the field frequently use patient reported measures as their primary endpoint. The constructs involved are complex and often demand multi-dimensional assessment including, for example, symptom intensity, distress and burden (8, 9). Qualitative research is uniquely placed to contribute to the understanding of such complex patient experiences.

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Conducting clinical trials is extremely expensive, and all efforts should be made to ensure the trial is equipped to answer its research question. Full attention must be devoted to planning, pilot testing and understanding the factors that influence trial feasibility, conduct and outcomes. Employing qualitative methods has the potential to enhance trial processes and improve understanding, thereby facilitating trial success (10-12). Yet while qualitative approaches are increasingly recognized as valuable in clinical trials, a systematic review has determined that they remain a very minor component (13). In their review of clinical trials registries, Clement et al (2018) determined that only 1492 studies (constituting just 0.24%, of registered trials) were incorporating qualitative methods. Trials using qualitative methods were more likely to be undertaken in Western, higher income countries and were more likely to be evaluating behavioural interventions (39%) rather than medications (5%), medical devices (5%) or surgical interventions (4%) (13). The authors highlighted that qualitative methods can make a contribution to drug trials, including an understanding of barriers to recruitment and the notion of equipoise, and noted that these possible advantages are not being exploited in the vast majority of clinical trials.

There is good guidance provided by the the MORECare (Methods Of Researching End of life Care) statements on integrating other research methods to enhance rigor in research that evaluates end of life care. The MORECare collaboration was formed to develop guidelines around identification, appraisal and a synthesis of 'best practice' research methods (14). These guidelines detail a series of recommendations to be addressed when conducting research that evaluates care that may be considered complex interventions at the end of life. The guidelines specifically highlight the opportunity for investigators to extend beyond traditional randomised controlled trials and encompass mixed methods into research design.

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While this provides helpful guidance, it doesn't specifically detail how qualitative research could be integrated into palliative care clinical trials.

We aimed to develop a practical framework that describes the contributions that qualitative research can make to a palliative care clinical trial.

Methods

A consensus process was adopted to develop an 'Integrating Qualitative Research into Clinical Trials Framework' ('Framework').

Participants: The Australian Palliative Care Clinical Studies Collaborative (PaCCSC) and Cancer Symptom Trials (CST) are national collaborative trials groups established to increase palliative care and cancer patients' access to multi-site phase 2 and 3 clinical trials, enable patients to benefit from clinical trial participation and increase the evidence base in palliative and supportive care (15, 16). These Collaboratives recognised that qualitative data would inform more robust trial design, complement the results of the trials, help elucidate the nature of challenges encountered during the conduct of the trials, point to potential solutions and help to inform implementing findings.

A Qualitative Research Subcommittee was established with the goal of facilitating trial design, conduct and implementation through incorporation of qualitative methods. The Qualitative Research Subcommittee consists of researchers from multiple disciplines, including medicine, nursing, occupational therapy, psychology, and social sciences. The research skills represented amongst its members span clinical trials, mixed methods, and qualitative designs.

Design: The framework was developed over 5 months in 2019 through a series of electronic discussions and successive refinement through telephone discussions at subcommittee meetings. This was supplemented with findings from a targeted review of the literature (11,

17-20) and expert opinion of the subcommittee members. The final framework was presented to researchers within the broader PaCCSC and CST collaboratives at their annual research forums, and feedback incorporated.

Content: During the consensus process, it was determined that the key requirement of the framework was that it should be practical, and its utility readily understood by clinical investigators collaboratively undertaking trial design. It was agreed that the design of the framework should assist clinical trialists to conceptualise, apply and realise the contributions of qualitative research to clinical trial outcomes.

The development of the framework was informed by a search of the literature. The structure for the framework is informed by the MORECare guidelines and applied according to the requirements for different phases or significant time points of the clinical trial (i.e. before the trial, during the conduct of the trial, and following the trial) (Refer Table 1). In addition, the framework identified questions that might be relevant to all phases of a clinical trial and can be incorporated at each time point. Samples of questions that might be asked of participants and health providers are also included for each time point. The list is not exhaustive and these questions should be regarded as examples.

[insert Table 1]

Discussion:

Despite the potential utility of qualitative research in clinical trials, it is infrequently used. The relative infrequent inclusion of qualitative researchers into trials teams is likely to be a contributory factor. In addition, Clement *et al* have suggested that this discrepancy between potential utility and actual use may be because qualitative research methods largely emerged from the social sciences and humanities disciplines, based upon interpretivist and constructionist epistemologies, and thus may be more readily applied to

research questions which seek to understand peoples' behaviours (13). This is in contrast to the dominant positivist epistemology in biomedical sciences and specifically randomised control trials, where quantitative data are more readily understood. A mechanism to facilitate the 'bridging' of epistemologies is required, embedding qualitative research in a meaningful way to enable both methods to co-exist and their contributions to be fully realised ~~and embed qualitative research in a meaningful way is required~~. Expanding clinical trial teams to include qualitative researchers represents a practical approach to providing such a bridge(21).

Meanwhile, t~~T~~he MORECare Guidelines provide a conceptual approach to such a bridge by promoting mixed methods research at all phases of complex intervention development and evaluation (22). Meanwhile a number of authors have offered 'real world' examples to target different key challenges within a trial such as maximising participant recruitment and retention (23-26). In developing our framework we believe we have provided a practical means of incorporating qualitative work across the landscape of clinical trial design and conduct. As such we present this as a pragmatic guide for clinical trial investigators.

A key area highlighted in our framework is the gathering of qualitative data before and during the conduct of the clinical trial in order to inform subsequent dissemination and implementation of the trial outcomes. This is an area not much discussed and yet important in the event of either positive or negative results in adequately powered, rigorously designed trials. When study participants have been asked for their views around dissemination of research results, they reported wanting the opportunity to access the findings and had firm views of how the findings should be presented (27). With due foresight, the study design can directly inform post study activities, and this would be welcomed by most researchers and participants, yet is often not considered in advance. Our

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framework provides a prompt to study designers to consider all these possibilities, and importantly facilitates the involvement of qualitative researchers early in the study design.

In proposing the current framework, we have drawn upon the available existing guidance along with the PaCCSC/CST Qualitative Research Subcommittee members' qualitative and trials research experiences. As such, the framework is not, and does not purport to be an empirically tested set of guidelines. Instead, it is a working document that may evolve and be adapted. A limitation of the framework is that it is primarily centred upon using interviews and focus groups as the main data collection approaches. Other approaches in qualitative research such as ethnography have a rich tradition and also potentially much to offer in understanding clinical trial outcomes. For example recording of discussions when a clinical trial is introduced and first discussed with a patient might yield useful information on the language that is least/most helpful to patients' understanding and to trial recruitment. More detailed incorporation of ethnography may be a focus of future iterations of this framework. Nevertheless the framework offers a strategy to consider the contribution of qualitative work across the spectrum of the life of the clinical trial including the implementation of findings.

Conclusion

A framework to assist those involved in clinical trial design is a helpful step towards greater inclusion of qualitative methods in clinical trials, which in turn, will improve understanding of trial processes, outcomes and implementation. A framework does not replace research rigor and the most productive and highest quality outcomes are likely to emerge from collaborations where qualitative researchers are core members of the clinical trial investigative team. The forming of truly multidisciplinary trial teams may indeed be the most important aspect to improving clinical trials and their results. Engaging with qualitative

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researchers and actively including qualitative methods into all elements of trial design represents an opportunity towards securing such outcomes.

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Table 1. A framework for identifying possible contributions that qualitative research might make to a palliative care clinical trial

Before the trial	
Potential contributions	Exemplar qualitative questions*
Measures: 1. Identifying the best primary and secondary endpoints for the trial (prioritising what's important to patients/families) 2. Understanding the nature of the problem (e.g. intensity/quality/other) 3. Selecting the best outcome measures 4. Selecting the best timepoints & frequencies for measures 5. Ensuring the full effects – both positive and negative – of the intervention are captured to enable estimation of net benefit	1. Patients: Thinking about this [problem] what is the most important thing that we should be focusing on improving? 2. Patients: Help me to understand what it is like having this [problem]. How would you describe it? Apart from how bad/strong/severe it is, are there other words you might use to describe it? What is the worst part of having [problem]? 3. Patients: Does this measure/question capture the thing that is bothering you? 4. Patients: When did you first notice improvement or worsening of this [problem]? How did it change over time? When / how often is the best time to measure [outcome]? HCP: When/how often should it be measured? 5. Patients: In what other ways has this [problem/treatment] has affected you? Can you tell me about any side effects from this [treatment]? How do you weigh up these side effects with any improvements you experienced in the problem we are treating? HCP: What are the best measures of adverse effects / negative outcomes to assist understanding of net benefit (or not) overall?
Sample: Optimising the eligibility criteria to: 1. Give the trial the best chance of identifying benefit if present. 2. Ensure generalisability of results to usual patients and practice	1. HCP: Which patients are most likely to benefit from this treatment? Is this the population you would normally use this medicine/treatment on? 2. HCP: Is this group representative? If not, in what way why not? Who is missing out? If we prove /disprove efficacy of treatment in this group, will that be useful to you as a clinician?
Study Procedures: 1. Understanding feasibility at potential trial sites 2. Optimising assessment of treatment fidelity / trial retention and attrition.	1. HCP: What (if any) problems do you think there might be with running this trial at your site: for patients? for HCPs? Prompts – for example, the symptom/problem not being common or perceived to be serious enough, the trial being burdensome, access to particular populations including particular language groups, other barriers to recruitment or retention, design problems [e.g. timing of measures], difficulty in receiving ethics or governance approval, lack of support from management or clinicians (e.g. due to not wanting to change usual care), insufficient research staff or expertise. 2. Patient: Do you have a preference for the way the intervention is delivered in the trial (e.g. frequency, duration, mode of administration) 3. HCP: What are the most important elements of adherence to this treatment? What important distinctions might there be between different kinds of drop-out?
Usual Care / Intervention: 1. Understanding the nature of usual care, including variation 2. Understanding the experience of the intervention / feasibility / acceptability of the intervention/treatment 3. Understanding the intervention/treatment and its putative mechanisms of action 4. Communication:	1. HCP: How do you normally treat this problem at your centre? HCP: To what extent do you think that different personnel treat the problem in different ways? 2. Patient: How do find having this treatment / intervention? What works well, what is more difficult? Patient: In what (if any) ways do you think this treatment is helping? What (if any) downsides do you think there are from this treatment? How likely are you to accept to have this approach at home - in clinical care? If using at home - in clinical care what would make it easier?

• Understanding how the study can best be communicated to patients and families within scripts for approach and participant information 5. Understanding likely translation	Patient: How willing would you be to take part in trial where you would have an equal and random chance of receiving either intervention X or an alternative Y? How willing would you be to complete measure X, Y, Z at intervals X, Y, Z? How willing would you be to stop using alternative treatments X, Y, Z while you are on the trial? HCP: How feasible / easy/difficult is it to provide or deliver this intervention? How does this compare with usual care in terms of ease of delivery? 3. HCP: How do you think this intervention works, and what do you think are the most important 'ingredients'? What should we measure apart from our outcomes to test hypotheses about possible mechanisms? 4. Patient: How should we talk about this study to patients and families? What are the useful words / language we should use? What are things we should not say? 5. Patient: What would you want your doctor to know about this intervention? What else would you want to have been told about this intervention? HCP: How likely would you be to use this intervention in patients if it were found efficacious?
During the Trial	
Study procedures: 1. Attrition, trial retention, burden and treatment fidelity 2. Trial conduct at site 3. Ethical conduct in the trial such as consenting processes	1. Patient: Of the instruments/questionnaires you are filling in, are there some that are much easier, much harder, too much/too little, do not make sense? Patient: What things are helping you in being part of this trial? What things are making it hard (harder) for you in being part of this trial? HCP: What difficulties with adhering to the treatment regime/intervention have you noticed? What factors have influenced patient attrition, retention? What have you noticed that may be burdensome for the patients participating in the trial? 2. HCP: What problems (if any) are you encountering with running this trial at your site: for patients? for health professionals? 3. Patient / HCP: In thinking about the consenting process, are there things that might make this easier for other patients in the future?
Intervention/usual care as delivered in the trial: 1. The nature of usual care 2. Understanding the magnitude and nature of expected improvement 3. Impact of intervention 4. View of intervention and its mechanism of action. 5. Population 6. Applicability to practice	1. HCP: In what way (if at all) is conducting this study having an influence on usual care delivery? 2. Patient: What do/did you hope for from the treatment? Did this happen? Did this treatment improve the thing that was most bothering you? What changed for you from having this treatment? 3. Patient: What is the impact of the intervention on your life? What is possible now? What is difficult? HCP: Are there any impacts that you have noticed on the patient's life as a result of the intervention? Of the trial? HCP: Do you have a view on what you think are the most important 'ingredients' of this intervention? 4. Patient: What problems [if any] are you encountering with using this treatment? HCP: What problems [if any] are you encountering with delivering this treatment? 5. HCP: Is this the population you would normally use this on? Who is missing out? Is this group representative? If not, in what way why not? 6. HCP: If we prove /disprove in this group will that be useful to you as a clinician? HCP: How likely would you be to use this intervention in patients if it were found efficacious?
After the trial	
Interpreting the results 1. Impact of intervention	1. Patient & HCP: What are your views of the results? Of the impact of the intervention? How do you view this result or feel about it? HCP: What factors other than the intervention might have influenced the measures?

	Patient & HCP: In hindsight, did we choose the best measures or were there other processes or outcomes we should have explored? If there were unexpected results, what could have caused them? HCP: What are your views of the impact of these results on practice going forward ?
Translation 1. Influence on practice already 2. Possible influence on future practice	1. HCP: How has the service changed following this result? What, if any, changes flowed on to the practice of people who weren't directly involved in the trial? What changes to the service's policies or procedures, or to workforce (e.g. roles or training) have occurred? 2. HCP: What might make you change your prescribing or practice around this issue? If practice has not changed, what degree of result would make it change? Or what else is missing that would have made you change practice? To what extent do you think this intervention could be extended to any populations or clinical contexts beyond those in the trial?
4. Questions relevant to all stages of trial conduct	
To be asked at each of the stages of the trial including at design, during conduct and following the trial. With adaptation the questions may be asked of participants and health providers.	1. Is there something that we have missed that you think we should know about? 2. Are we measuring or asking you about the most important thing for you at the moment? 3. Are there other domains or areas we should be considering, not covered today?

HCP = health care professional *Many of the questions asked of patients, with adaptation, could also be asked of caregivers.