User's Guide to Research in Palliative Care: Why Is a New Series Needed?

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Introduction

THIS PAPER SERVES as an introduction to an upcoming series in the *Journal of Palliative Medicine* on research methods in palliative care. The goal of the series is to enable the *Journal of Palliative Medicine* readership to become more critical readers of the increasingly complex methods used in palliative care research. Our aim is not to provide a "how to" for the use of various research methods (as such an undertaking requires far more than a six-article journal series), but rather to provide information to promote critical evaluation of the research methods currently used to shape and advance our practice.

The development of the evidence base for palliative care now encompasses far more than quantitative experimental research methods. Not only are quasi-experimental and observational research methods increasingly utilized, qualitative research methods are providing valuable insights into palliative care. For example, the 2008 annual conference of the American Academy of Hospice and Palliative Medicine had more than 150 attendees in the research methods seminars on topics such as observational research and qualitative data analyses and such seminars were ranked among the highest by attendees. As the evidence base for palliative care builds, it is imperative that there be a broad-based understanding of the research methods used to develop this evidence base. We have chosen to focus on research methods outside of experimental methods and the randomized controlled trial (RCT) because alternative methods have become increasingly necessary to study the complex aspects of palliative care delivery. Accordingly, this series will cover the following topics: an introduction to observational and quasi-experimental research methods, the challenges of observational and quasi-experimental research including selection bias and confounding, the rationale for and meaning of analytic techniques such as instrumental variable analysis and hierarchical modeling, meta-analysis, and qualitative research methods.

Why is This Series of Articles Needed?

The importance of understanding, evaluating, and utilizing research methods that extend beyond the randomized

controlled clinical trial is highlighted by a recent high profile systematic review¹ published in the *Journal of the American Medical Association* that examined the impact of palliative care consultation on patient, family, and utilization outcomes. The authors of this rigorously conducted systematic review concluded that there was no evidence to support the hypothesis that palliative care teams improved outcomes. Whereas this review followed accepted methods and the paper's findings flowed logically from its analyses, the authors' premise that the only studies appropriate to examine the research hypothesis were RCTs was not only fundamentally flawed but led to inappropriate and incorrect conclusions. In the following section, we illustrate, using the research question from the recent *JAMA* article¹ (i.e., do palliative care teams improve outcomes) as an example, why palliative care researchers and clinicians need to understand and employ research methods beyond the RCT.

The Strengths of the RCT

The RCT is the strongest design to test efficacy: whether treatment is better than placebo or other alternative under ideal conditions. The RCT's strength lies in the fact that subjects are randomly assigned to the treatment or control group. Randomization minimizes confounding by observed and unobserved factors. That is, it increases the likelihood that the groups will be comparable both in terms of variables that we identify and can measure, and in terms of variables that we may not identify or cannot measure but that are likely to be associated with the outcome of interest. Furthermore, the use of randomization removes subjective biases of the investigators, either overt or covert, that may be introduced into the process of selecting patients for the treatment or control group. Thus, RCT's have excellent internal validity in that differences in outcomes between groups can be attributed to the treatment.

The Limitations of the RCT and the Need for Alternative Designs

Despite the strengths of RCT's, there are certain research questions, particularly in palliative care, for which an RCT may be unnecessary (because the question has been clearly

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answered by observational studies, e.g., morphine for pain); inappropriate; impossible; or inadequate.^{2,3} In such cases, the use of observational or quasi-experimental designs may be more appropriate to answer the questions of interest.

An RCT may be inappropriate

In some situations, RCTs may be inappropriate because the very act of randomization may reduce the intervention's effectiveness. Such situations can arise when the intervention's effectiveness depends on the subject's active participation which, in turn, depends on the subject's beliefs and preferences.^{2,3} For example, outcomes from an RCT of palliative care consultation are largely dependent on physicians following the palliative care team's recommendations. Whereas physicians might agree to randomization of their patients, physicians receiving mandatory, unrequested, and unwanted consultations for their "intervention" patients are unlikely to follow such recommendations. Indeed, studies that have attempted to randomize patients to mandatory medical consultation outside of palliative care⁴⁻⁸ have reported low compliance rates (<70%) with treatment recommendations. In contrast, studies of requested consultation, which mirrors the real world environment, have reported relatively high compliance with treatment recommendations (>80%).^{9,10} An RCT that randomizes patients to an unwanted intervention that results in no treatment is likely to be biased toward a null finding as was observed by Zimmermann et al.¹

An RCT may be impossible

Although some argue that any intervention can be subject to an RCT, such a view ignores a number of serious real world obstacles.² Most prominent of these is the fact that treating physicians are reluctant to have their patients enroll in a trial in which one of the treatment groups contrasts with their own beliefs and practice styles. For example, despite the fact that a majority of urologic surgeons in England stated that they believed that an RCT was needed to determine the impact of surgery on stress incontinence, none would agree to participate in such a trial because of their beliefs in the correctness of their own practice style.¹¹ This situation is even more common in palliative care where strong diametrically opposed physician beliefs about palliative care (e.g., it would be unethical to deny patients palliative care versus patients do not require palliative care and it could cause harm) limit patient enrollment in RCTs. In a prior RCT that we performed of palliative care consultation for patients with dementia,^{12,13} over 30% of physicians would not consent to have their patients enrolled in this study because they did not want them to receive palliative care. Similarly, in a recent unpublished survey of 27 oncologists conducted at our institution, 45% stated that they would not allow their patients to be randomized to a trial of palliative care consultation. Thus, although "collective equipoise" may exist, the absence of "individual equipoise" hampers the conduct of an RCT and results in considerable enrollment bias.²

An RCT may also be impossible due to contamination or crossover of subjects from one treatment group to another. A recent RCT of ethics consultation in intensive care units reported that 35% of subjects in each study arm crossed-over.¹⁴ As in the ethics consultation study, physicians who

gain experience with a beneficial intervention (i.e., palliative care, ethics consultation), either because of their experience in the trial or as a result of experiences outside the trial, are likely to request the intervention for their patients who are randomized to usual care. Similarly, family members and patients themselves may also request the intervention. In these situations, commonly used "intent to treat" or "as treated" analyses will produce biased estimates of the treatment effect toward the null hypothesis.¹⁵

An RCT may be inadequate

Finally, the external validity or "generalizability" of RCTs may be low in certain situations and additionally may not be able to answer important research questions. Using Zimmermann and colleagues¹ systematic review as an example, the external validity of an RCT for palliative care consultation will be low for three reasons. First, it is likely that physicians who would allow their patients to participate in an RCT would be unrepresentative of most practicing physicians for reasons detailed above. Second, mandatory palliative care consultation within an RCT does not reflect real-world practice patterns of medical care in the United States where mandatory consultation is unusual and unwelcome to practitioners. Finally, patients and families who agree to randomization or enrollment in a study may be atypical.² For example, we recently attempted to study patients' perceptions of implantable cardioverter device (ICD) deactivation and circumstances under which patients would consider having their ICD deactivated. We were unable to enroll a single patient in this quantitative study because of their discomfort with the topic. Similarly, patients who are willing to enroll in a study of palliative care consultation are likely to be non-representative of the real-world population. Thus, even if one were able to perform an RCT, the results are unlikely to be generalizable to the at-risk population writ large.

Overview of the Series

The preceding discussion demonstrates the necessity of alternatives to the RCT for palliative care research. In situations where an RCT is not appropriate, adequate or possible, observational, quasi-experimental, and qualitative research have proven to be valuable tools. The forthcoming series of articles will provide a detailed reader's guide to these research designs and newly developed analytic methods that are being increasingly utilized to reduce bias from nonrandom selection and to strengthen inferences resulting from these types of studies. Fourteen of the leading researchers in palliative care in the United States have graciously agreed to coauthor a set of articles that will appear every other month in the *Journal* for the next 12 months. The outline for this series is as follows:

Article 1: "Study Design, Precision, and Validity in Observational Studies"

Drs. Carlson and Morrison will provide an introduction to observational and quasi-experimental designs. Observational studies draw inferences about the effect of a treatment on subjects, where the assignment of subjects into groups is observed rather than manipulated (e.g., through randomization) by the investigator. Quasi-experimental designs are

similar to experimental designs in that there is a specific intervention for the “treated” group, but lack the randomization of subjects to treatment and control groups. This paper will introduce the major types of observational and quasi-experimental study designs, discuss their challenges and limitations, and provide practical insights into how to evaluate critically studies employing these designs in the palliative care literature.

Article 2: “The Challenge of Selection Bias and Confounding in Palliative Care Research”

Drs. Helene Starks, Paula Diehr, and J. Randall Curtis will describe the major challenges in observational research: selection bias and confounding. Selection bias and confounding generally arise due to nonrandom assignment to treatment (or exposure) groups according to unmeasured characteristics. This results in systematic differences between treatment groups in prognosis or responsiveness to treatment, rendering inferences about the effect of treatment (or exposure) to be biased. The authors of this paper will discuss why selection bias and confounding are problematic and the methods used to address them, including multivariate modeling and propensity score analysis.

Article 3: “When and How to Consider an Instrumental Variable in Palliative Care Research”

Drs. Nathan Goldstein, Partha Deb, and Joan Penrod will introduce instrumental variables models as a means of attempting to address treatment effects due to variables that can't be measured easily. This method is needed particularly in palliative care research given the complexities with accessing, enrolling, and collecting data on ill patients with chronic disease. Given a well-chosen instrumental variable, an estimate of the treatment effect can be accomplished even if there are unmeasured factors influencing the association between the independent variables and the outcome. The authors will describe instrumental variables estimation, criteria for choosing appropriate instrumental variables, and discuss examples of instrumental variables that are increasingly used in palliative care research.

Article 4: Introduction to Hierarchical Modeling”

Drs. Howard Degenholtz and Namta Bhatnagar will outline the conceptual basis for using hierarchical modeling in palliative care research. Hierarchical linear modeling (or “multilevel analysis”) allows variance in outcome variables to be analysed at multiple hierarchical levels. For example, data are often considered as patients nested within physicians nested within hospitals. Hierarchical modeling allows one to estimate the variance in an outcome at the patient, physician and hospital levels. With simple examples, the authors of this article will demonstrate the importance of accounting for variation at different “levels” of the analysis and will provide an overview of how to interpret results of a hierarchical model.

Article 5: “How to Conduct Meta-Analyses”

Drs. Wendy Anderson and Robert Arnold will describe the methods used to conduct meta-analyses and how to interpret the results of meta-analysis (i.e., central tendency and

variability). A meta-analysis statistically combines the results of several studies that address a shared research hypotheses and is increasingly used in palliative care research. This paper will discuss when meta-analyses are useful and will review the major meta-analyses that have been conducted in the field of palliative care to date.

Article 6: “Beyond Numbers: The When, Why and How of Qualitative Research”

Drs. Karen E. Steinhauser and Julie V. Barroso will describe how qualitative research methods have been used in palliative care research. Qualitative research aims to gather an in-depth understanding of human or organizational behavior and is generally exploratory in nature (i.e., hypothesis-generating). The authors of this article will outline the types of research questions that are appropriate for qualitative research in palliative care and provide an overview of qualitative research methods including sample selection, interview techniques, and the coding and analysis of qualitative data. The paper will discuss the advantages and limitations of qualitative research methods and discuss recent findings in the field of palliative care.

In summary, we hope that the readers of the *Journal of Palliative Medicine* will find this series helpful in interpreting and building the evidence base of palliative care. The increasing use of observational and quasi-experimental research methods in palliative care research requires an informed and engaged community willing to challenge and advance the methodologies on which the evidence base for palliative care is being built. We hope you find this series informative, thought-provoking, and helpful and we look forward to your further thoughts and suggestions.

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