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A SMART design to optimize treatment strategies for patient and family caregiver outcomes

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ABSTRACT

Sequential multiple randomization trial (SMART) designs are experimental designs used to identify treatment strategies that maximize targeted health outcomes. SMART designs are receiving greater attention in nursing and other health disciplines to develop multicomponent interventions that are tailored to the patient's (or family caregiver's) needs and preferences. A SMART design resembles a traditional randomized controlled trial (RCT) design in that it scientifically examines intervention effects with randomization. However, the two designs address very different research inquiries. In this article, we compare traditional RCT designs and SMART designs, describe the adaptive treatment framework that underlies SMART designs and key features of SMART designs, and illustrate the application of a SMART design to develop an adaptive palliative care treatment to improve patient and caregiver outcomes.

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Introduction

Traditional randomized controlled trials (RCTs) have long represented the gold standard for evaluating intervention efficacy because the design helps minimize selection bias and other common sources of bias (Pocock, 1991; Schulz, Altman, & Moher, 2010a). Nonetheless, there are shortcomings in traditional RCT designs. Consider that effective treatment for many patient problems requires the use of more than one intervention. For example, effective self-management of a symptom may require both prescription medications and cognitive behavioral interventions such as guided imagery. In addition, many interventions designed to improve patient and/or family caregiver outcomes are actually comprised of multiple components (e.g., both medications and exercise) and/or may involve elements that are tailored to the patient's needs or preferences (Conn, 2012; Northouse, Katapodi, Song, Zhang, & Mood, 2010; Schulz, Czaja, McKay, Ory, & Belle, 2010b).

However, what is tested in a traditional RCT is the effect of the intervention as a whole; the components (e.g. medications and imagery) or the intensity/dose delivered to individuals in the intervention group may be measured as part of fidelity monitoring, but the effects of the components or the decisions underlying

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the determination of components and intensity cannot be directly tested in traditional RCTs. Thus, although a traditional RCT design allows for rigorous testing of an intervention's efficacy or effectiveness, it provides limited data to develop "treatment strategies", where such strategies may involve a number of different interventions, a number of different doses, or different components of previously tested interventions. Although nomenclature may vary across disciplines, an adaptive treatment strategy (or an adaptive treatment or dynamic treatment regimen) refers to a set of decision rules for choosing interventions for individual patients that specify whether, how, and when to alter the type and dosage of interventions in the course of treatment (Almirall, Compton, Gunlicks-Stoessel, Duan, & Murphy, 2012; Dawson & Lavori, 2015; Murphy, 2003). Note that we are using the term treatment and treatment strategy to refer to the overall care that the patient receives, whereas the term intervention refers to single intervention.

With the recognition of limitations of traditional RCTs, sequential multiple randomization trial (SMART) designs are receiving greater attention in nursing and other health disciplines. Proposed by Murphy et al. (Collins, Nahum-Shani, & Almirall, 2014; Murphy, 2003, 2005; Murphy, Lynch, Oslin, McKay, & TenHave, 2007; Nahum-Shani et al., 2012), SMART designs are an experimental design used to identify treatment strategies that maximize targeted health outcomes. The central tenet underlying SMART designs is that to be effective, treatment must be responsive and adaptive to individuals' changing needs and responses over time, and a study design to develop such a treatment strategy must be closely reflective of the way treatment evolves over time in clinical practice. In this article, we compare traditional RCT designs and SMART designs. We describe the adaptive treatment framework that underlies SMART designs and key features of SMART designs and illustrate the application of a SMART design to develop an adaptive palliative care treatment strategy to improve patient and caregiver outcomes.

Fixed Treatment Framework vs. Adaptive Treatment Framework

Traditional RCT designs are based on a fixed framework in which interventions are fixed in composition and intensity (Murphy, 2003). In traditional RCTs, all participants who are randomized to an intervention group receive the same intensity and the same intervention components whether the particular participants need all of those components or not (Collins, Murphy, & Bierman, 2004; Murphy, 2003). In this framework, the various needs of individuals may not be met optimally by interventions that are fixed in composition and intensity. In addition, providing fixed components to all participants may not be practical or may be too costly. Such problems may lead to nonadherence and dropout because not every component is needed or valued by everyone, thus jeopardizing intention-to-treat comparisons between the intervention and control groups (Collins et al., 2004; Dawson & Lavori, 2015). The traditional RCT design does not fit comfortably with management of chronic conditions in actual clinical practice where an effective treatment strategy frequently requires a sequence of interventions adapted to an individual's responses (Collins, Murphy, & Strecher, 2007).

Adaptive treatments have emerged as a new paradigm for building evidence for managing chronic conditions that involve waxing and waning trajectories (Brooner & Kidorf, 2002; Connell, Dishion, Yasui, & Kavanagh, 2007; Lavori, Dawson, & Rush, 2000; Unutzer et al., 2001). In the adaptive treatment framework, outcomes are optimized with tested treatment strategies that can guide treatment decisions in terms of the intensity of interventions, the type of intervention, or the combination of more than one intervention based on individuals' responses to an initial or previous intervention (Murphy, 2005). Such adjustments result in treatment strategies that are based on decision rules that link characteristics of the individual, e.g., sociodemographic characteristics, preferences, and responses to interventions, with specific types of intervention components and levels of intensity (Collins et al., 2004). Accordingly, there can be different treatment strategies that are comprised of different compositions and intensity of an intervention (or a combination of intervention types) delivered across individuals and within individuals over time.

This adaptive treatment framework resembles clinical practice in the sense that it involves the modification of treatment in light of the patient's response over time, but an important difference is that in clinical practice the decision rules involved in sequencing interventions are typically rather implicit even when clinicians follow relevant clinical guidelines and are, therefore, difficult to replicate. To build evidence regarding the efficacy of those strategies, the decision rules must be made explicit for evaluation (Collins et al., 2004). In the adaptive treatment framework, decision rules are put to a test by randomizing the patient/participant when critical questions arise, such as "What should I do when a patient is not responsive to the initial intervention? What should be the next step in the overall treatment plan?"

With these differences in the frameworks underlying study designs in mind, it is important to note that a traditional RCT and a SMART ask different research questions. A traditional RCT is designed to test the efficacy or effectiveness of an intervention compared to a parallel control condition (Pocock, 1991). On the other hand, a SMART is not to establish the efficacy of an intervention but to generate data on how to optimize treatment, particularly focusing on identifying treatment strategies to address nonresponsiveness to an initial or previous intervention (Almirall, Nahum-Shani, Sherwood, & Murphy, 2014).