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Conducting a two-stage preference trial: Utility and challenges

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ABSTRACT

Treatment preferences reflect individuals' choice of therapy and influence their adherence to treatment and achievement of outcomes. The two-stage partially randomized clinical or preference trial (two-stage PRCT) is an appropriate design for examining the contribution of treatment preferences. It involves a two-stage process for assigning participants to treatments, which is useful to dismantle the effects of the treatments from those of treatment preferences. In this paper, we explain the role of treatment preferences in intervention evaluation research, describe the protocol for implementing the two-stage PRCT, and discuss issues in its application. The issues are encountered in the selection of treatments, assignment of participants and assessment of treatment preferences. Lastly, we propose ways to address the issues.

What is already known?

- Participants' preferences for treatment influence enrollment in intervention research, adherence to treatment, and outcomes.
- Accounting for preferences in treatment allocation, an essential element of patient-centered care, improves treatment adherence, satisfaction and outcomes.
- The two-stage preference trial is a research design used to examine the unique contribution of the intervention and of preferences.

What this paper adds?

- The protocol for implementing a two-stage preference trial is described.
- Issues in the conduct of the two-stage preference trial are discussed.
- Strategies to address the issues are proposed.

1. Introduction

Preferences for treatment represent individuals' choice of treatment (Stalmeier et al., 2007), that is, the treatment they desire to prevent illness, promote health or manage a presenting health problem. Treatment preferences are of clinical importance: they are a core element of patient-centered care defined as care that is sensitive and responsive to the person's needs and preferences (Bokhour et al., 2009). Patient-centered care involves: providing

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persons with information on treatments available to address the presenting health problem; assessing their treatment preferences; and providing the treatment that is congruent with their expressed preferences (Givens et al., 2007). Whereas patient-centered care has been associated with enhanced engagement and adherence to treatment (e.g. Lee and Lin, 2010), increased satisfaction with care (e.g. Bertakis and Azari, 2010), and improved physical and psychological functioning few researchers have examined the contribution of treatment preferences to patient-oriented outcomes.

The two-stage preference or partially randomized clinical trial is considered an appropriate design for examining the contribution of treatment preferences to adherence and outcomes in intervention evaluation research (Sidani et al., 2009a). However, planning and conducting a two-stage partially randomized clinical or preference trial (two-stage PRCT) present some challenges. In this paper, we explain the role of treatment preferences in intervention evaluation research, describe the protocol for implementing the two-stage PRCT, and discuss and illustrate issues in its application with examples from our work (1).

2. Role of treatment preferences in intervention evaluation research

Just like patients seeking care, persons contemplating enrollment in an intervention evaluation study acquire knowledge of different treatments to manage their presenting health problem. Sources of treatment-related knowledge include media; discussion with family, friends and healthcare professionals; personal experiences; as well as the process of obtaining informed consent for the trial. Participants' understanding of what the treatment is about, how it is delivered, and its benefits and risks shape their preferences. Results of descriptive and experimental studies show that most ($\geq$60%) participants indicate preferences for the treatments under investigation (e.g. King et al., 2005; Preference Collaborative Review Group, 2009).

Persons with preferences may decline enrollment in an intervention evaluation study in which the method of treatment allocation does not account for their preference. These persons may resent being randomly assigned to a treatment and may not be willing to take the risk of being allocated to the non-preferred treatment (Floyd and Moyer, 2010). In their systematic review, King et al. (2005) estimated the percentage of participants who refuse randomization to be up to 74%. With this large percentage of persons potentially declining enrollment, the accrued sample size is small, leading to low statistical power to detect significant intervention effects.

Alternatively, persons with preferences may enroll in an intervention trial because they view their participation as an opportunity to receive the preferred treatment. If the method for allocating participants to treatment does not account for participants' preferences, then two subgroups are formed within each treatment condition. The first subgroup consists of participants who are randomly allocated to the preferred treatment. These participants are likely to be satisfied with the treatment they receive, motivated to engage and adhere to treatment, and consequently experience improvement in the outcomes (Lewis et al., 2006). The second subgroup involves participants randomly assigned to the non-preferred treatment. They are likely to be disappointed because they do not get the treatment they desire. Therefore, some of these participants may withdraw from the study and others may no longer be motivated to engage and adhere to treatment (Leykin et al., 2007) and may show no or minimal improvement in outcomes (Sidani et al., 2009a). The influence of treatment preferences on attrition, adherence to treatment, and outcomes is supported empirically. The results of two meta-analyses (Preference Collaborative Review Group, 2009; Swift et al., 2011) demonstrated lower attrition rates for participants allocated to a treatment that was congruent (compared to incongruent) with their preference. The findings of five studies consistently showed that participants assigned to their treatment of choice were more engaged and adhered more to the treatment compared to participants assigned to a non-preferred treatment, (Bedi et al., 2000; Janevic et al., 2003; Kwan et al., 2010; Macias et al., 2005; Raue et al., 2009). The effects of treatment preferences on outcomes were estimated in two meta-analyses; the mean effect size ranged between .15 (Preference Collaborative Review Group, 2009) and .31 (Swift et al., 2011). Although the effect sizes were small, they implied greater improvement in outcomes for participants assigned to the preferred, as compared to non-preferred, treatment.

In summary, accounting for treatment preferences is beneficial in practice and research contexts. Empirical evidence indicates that providing treatment congruent with participants' choice reduces treatment and trial withdrawal, promotes treatment engagement and adherence, and improves outcome achievement. This evidence highlights the importance of investigating the influence of treatment preferences in enhancing the validity and clinical relevance of conclusions in intervention evaluation research.

Three types of designs have been proposed to examine the effects of treatment preferences: the randomized clinical trial, the preference or partially randomized trial, and the two-stage PRCT. The two-stage PRCT, described next, is identified as the most appropriate design for determining the impact of treatment preferences because it enhances groups' comparability at baseline, thereby controlling for variables that may confound the effects of either the intervention or preferences and dismantling the contribution of preferences from that of treatments (for details, refer to Sidani et al., 2009a).

3. Protocol for implementing the two-stage PRCT

The two-stage PRCT was initially proposed by Rücker (1989) as a design to dismantle the influence of preferences from that of the intervention on outcomes. Similar to an experimental or randomized clinical trial (RCT), the two-stage PRCT involves the assignment of eligible, consenting participants to the treatments under investigation, and the measurement of outcomes before and after implementation of the treatments. What