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A Targeted Literature Review of Patient Perspectives of Placebo Use in Clinical Trials: How can the Patient Voice Inform with Trial Design, Recruitment, and Retention?

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Introduction

- The double-blind, placebo-controlled randomized clinical trial is considered the “gold standard” design to determine drug efficacy, especially when no alternate treatment is available[2,7]
- However, patients may view the chance of being randomized to placebo negatively, potentially contributing to slow recruitment or eventual attrition[1]
- We conducted a targeted literature search to better understand the patient perspective on the use of placebos in clinical trials

Objective

- Develop patient-centered suggestions for conducting and retaining participants in placebo-controlled trials

Methods

- Embase, Medline, and Google Scholar were used to identify qualitative studies and literature reviews describing patient perspectives, views, and attitudes of the use of placebos in placebo-controlled trials
- Our search included the following parameters:
  - Keywords: placebo, clinical trial, attitudes/views/experiences (with the term ‘patient’), qualitative, interviews, focus groups, surveys
  - Dates: Database inception to November 2024
  - English-language
- Articles were excluded if they met the following criteria: did not describe patient perspective, no qualitative analysis, open-label studies, clinical practice
- Of the 49 abstracts identified, 20 met inclusion criteria for full-text examination (See Figure 1)
  - 15 qualitative research studies
  - 5 literature reviews

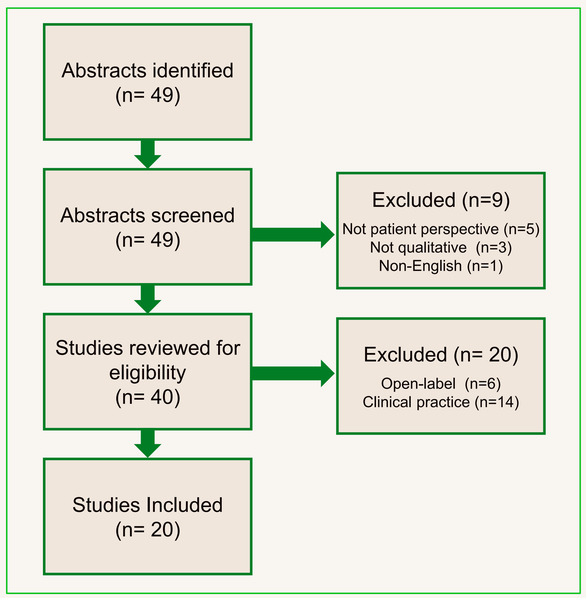

Figure 1. Flow diagram of the literature review process

Results

- Patient perspectives on the use of a placebo arm in a clinical trial are varied and complex based on:
  1. Disease/Condition[5,9]
  2. Severity of Symptoms[9]
  3. Overall Understanding of Placebo Treatment[2,6,7]
- Patient understanding of the placebo effect may impact trial recruitment and retention or even the results **(Figure 2)**
  - Patients (and caregivers) who fear that not receiving medication may negatively impact well-being are reluctant to participate in trials with a placebo group[1]
  - Participants may withdraw from a trial if they believe that they are receiving a placebo[1]
  - Participants may be hyperaware of the placebo effect and/or may alter/adjust their responses in attempt to account for it[10]
  - However, there are mitigation strategies researchers can use to minimize these potential negative impacts **(Figure 3)**
- Participants may experience cognitive dissonance when reconciling their experience during the trial with the knowledge that they did not receive active treatment **(Figure 4)**

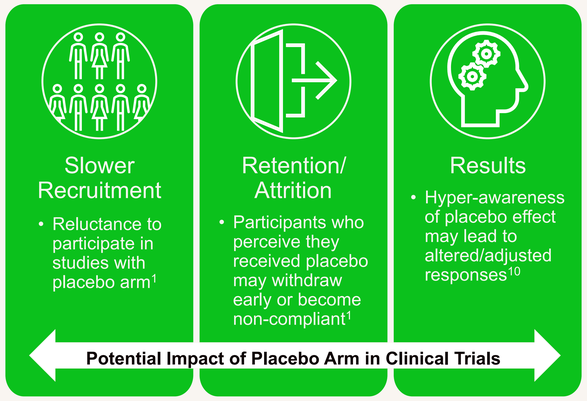

Figure 2: Potential Negative Effects of Including Placebo Arm

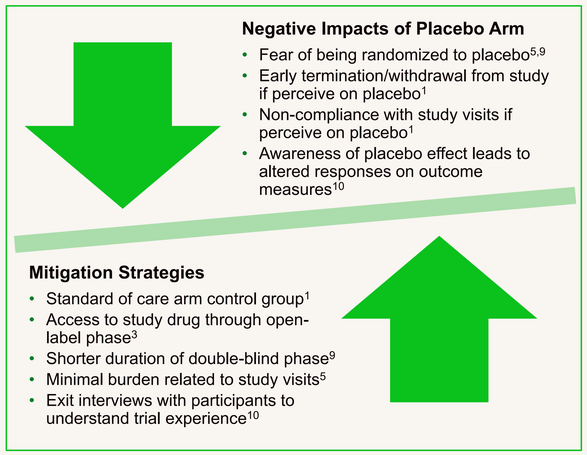

Figure 3: Mitigation Strategies for the Potential Negative Effects

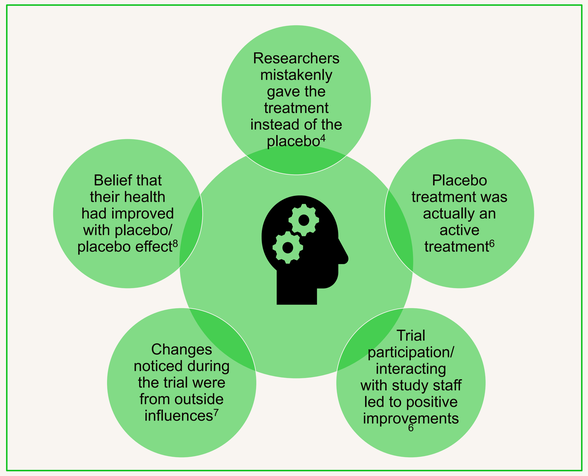

Figure 4: Participants’ Cognitive Dissonance Regarding Assignment to Placebo Arm

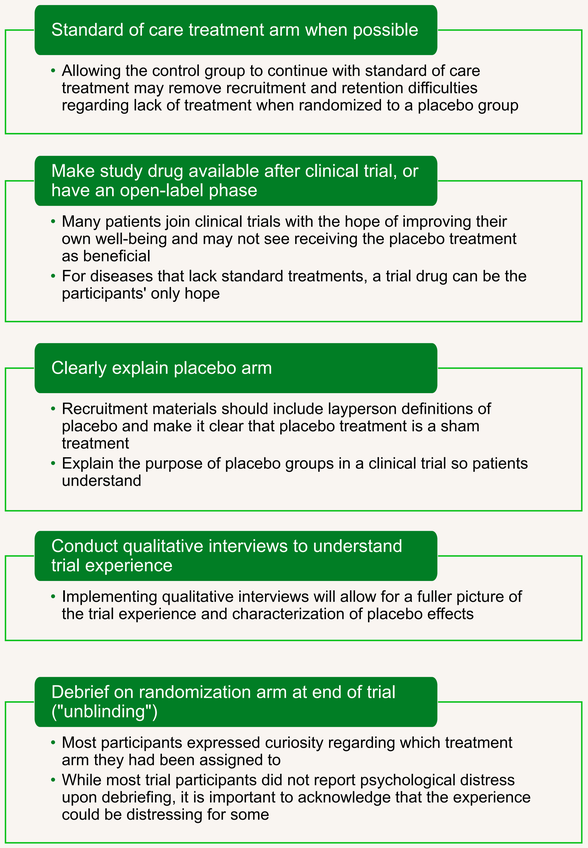

Figure 5: Recommendations for Future Trials

Recommendations

- Figure 5 details patient-centric approaches to mitigate the potential negative effects of inclusion of placebo arms in clinical trials.
- Consideration should be given to the following:
  - Use standard of care treatment arm as the control group when possible
  - Offer access to the study drug after trial completion or include open-label phase
  - Provide clear, easy-to-understand information about placebo treatment and the role of a placebo arm in recruitment materials
  - Conduct qualitative exit interviews with participants to understand trial experience and better characterize placebo effects
  - Unblind and debrief participants on randomization arm at the end of a trial

Conclusions

- The patient view of the use of placebos in clinical trials is nuanced and dynamic.
- Drug developers would benefit from an appreciation of patients’ views of placebos within the context of use and incorporation of patient-centered approaches to attenuate participation barriers related to placebo randomization.

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Disclosures

SB, KW, EM are employees of Fortrea, Inc.

KJ and CC were employees of Fortrea, Inc. when the literature review was conducted.

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