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Risks of Clinical Research Must Be Reasonable and Necessary

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A central ethical issue in evaluating a clinical trial is whether a study's scientific and clinical value justifies the risks and burdens imposed on research subjects. We are doubtful that this justification is present for the proposed randomized clinical trial (RCT)—at least as the study's rationale and design are described.

VALUE OF THE CLINICAL TRIAL

The proposed study asks whether treating prediabetic patients who have moderate to severe obstructive sleep apnea (OSA) with positive airway pressure (PAP) therapy, along with lifestyle coaching, will decrease the risk of converting from prediabetes to diabetes. The trial provides an opportunity to establish proof-of-concept that OSA contributes to the development of diabetes, and a positive result might eventually reinforce the use of PAP therapy among prediabetic patients with OSA. However, the study's value is limited by two factors.

First, since the trial participants have both prediabetes and moderate to severe OSA, PAP is already an indicated treatment for all trial participants (Qaseem et al. 2013). Thus, even a positive result is not likely to alter clinical practice substantially because it will not expand the group of patients indicated to receive PAP therapy. Second, this trial uses a run-in period to identify participants who are most likely to adhere to PAP therapy, in order to boost observed PAP effects (if any). This limits the study's generalizability because in ordinary practice, clinicians will not face only those patients who are likely to use PAP.

We therefore wonder how much clinical value this study adds. At best, a positive trial result might reiterate the benefits of PAP therapy or assess a pathophysio-logical hypothesis about PAP therapy for prediabetics with OSA. However, it is not clear that the proposed design is appropriate, given these limited goals.

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RISKS OF RESEARCH PARTICIPATION

In this trial, clinical equipoise exists for prediabetes but not for OSA. In fact, when considering prediabetes alone, the risk/benefit ratio of participation seems favorable since all participants will receive lifestyle coaching (a standard intervention for prediabetes), and risks associated with PAP therapy are low (Qaseem et al. 2013).

When considering OSA, however, the risk/benefit ratio is more complicated. Because PAP therapy is an indicated treatment for all participants, it is important to consider the risks the control participants will take on by forgoing PAP therapy for the duration of the trial. For patients with moderate to severe OSA, forgoing PAP therapy means forgoing its potential benefits such as improvements in blood pressure, daytime sleepiness, memory, and daily functioning (Qaseem et al. 2013). There are also emerging data showing that PAP therapy may decrease one's risk of serious cardiac morbidity and mortality among those with OSA if they maintain high adherence to the therapy. Although observational studies have shown mixed results, some have shown significant reductions in mortality with PAP therapy (Qaseem et al. 2013). A recent international multicenter RCT did not find significant effects of PAP therapy on risk of cardiovascular events or mortality (McEvoy et al. 2016), but limitations of the trial (such as low PAP adherence rate in the intervention arm) may have decreased its ability to detect possible mortality differences (Mokhlesi and Ayas 2016). A large 2-year RCT in Greece comparing standard PAP versus an intensive PAP (to increase adherence) showed—even compared to an active PAP arm—that higher adherence among the intensive PAP group resulted in significantly fewer deaths and hospitalizations (Bouloukaki et al. 2014). Even if the data are not yet definitive, if the proposed RCT identifies persons with OSA who are willing to use PAP with a high likelihood of adherence, then asking them to forgo its use would mean asking them to risk higher rates of serious morbidity and mortality.

It is worth emphasizing that the risks faced by the trial participants are amplified by the use of a run-in period. The selected patients are those most likely to benefit from PAP therapy. Consequently, the selected participants (compared to a standard OSA population) are at greatest risk of forgoing significant clinical benefits if placed in the control arm.

PERMISSIBILITY OF FORGOING EFFECTIVE TREATMENT IN CLINICAL TRIALS

Even if the control arm does face greater risk of negative events, does this risk exceed what should be allowed in a clinical trial like this one? The debate over the use of placebos in RCTs when effective treatments exist provides a framework for considering the permissible level of risk study participants can be asked to take on. Considerable debate exists about the exact threshold of permissible risk in such situations, but there is agreement that the use of placebos (or otherwise untreated controls) is unethical if it would increase risk of mortality or serious, long-term morbidity (Emanuel and Miller 2001; Temple and Ellenberg 2000), while some also include the risk of severe discomfort or serious but reversible harm (Emanuel & Miller 2001).

CONCLUSIONS AND RECOMMENDATIONS

With the limited information provided in the case report (e.g., it is not clear how long the intervention period is), it is not possible to provide conclusive recommendations. We therefore highlight issues that the investigators and their institutional review boards should consider.

First, are the control-arm subjects being asked to forgo likely reduction in risk of serious morbidity and mortality? There is some evidence to suggest this to be the case. Independent expert input should determine this issue. If the answer is affirmative, then by any account, the study goes beyond the currently accepted level of permitted risk in RCTs. Further, the no-PAP control arm cannot be justified by the reasoning that “they aren’t getting the treatment outside the RCT anyway.” Once these participants are identified and are allocated to the control arm, they are taking on risks attributable to research since the investigators are controlling the allocation of interventions. After all, the investigators do not know whether those patients would in fact have gone on to receive PAP outside the trial, even if, at the time the participants were identified, they were not receiving PAP.

Second, even if it is debatable whether the risks to subjects would involve increased morbidity and mortality, IRBs must determine whether the risks and burdens are justified by the benefits, and whether the risks are minimized in pursuing the scientific question. At least as currently described, the scientific and clinical value of the proposed RCT seems limited—even positive results will not likely change clinical decisions. Further, the mandate to minimize research risks probably requires that other trial designs be considered to answer the scientific question, for example, by “piggybacking” on to a larger PAP therapy trial or by using a different type of control arm (similar to Bouloukaki et al. 2014).

The proposed study could provide interesting insights into the relationship between PAP therapy and the development of diabetes. However, the trial’s clinical value seems limited, especially when considering the potential risks that participants in the control arm would be taking on by forgoing PAP therapy. This concern is increased by the “enrichment” of the sample to those who are likely to use, and therefore benefit from, PAP therapy.

Acknowledgments

DISCLOSURES

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