From efficacy to safety concerns: A STEP forward or a step back for clinical research and intercessory prayer?: The Study of Therapeutic Effects of Intercessory Prayer (STEP)

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> "Historically one is inclined to look upon science and religion as irreconcilable antagonists... I maintain that cosmic religious feeling is the strongest and noblest incitement to scientific research..." *Einstein, A. The World as I See It*

Systematic study of intangible "noetic[1]" or "frontier[2]" healing methods such as intercessory prayer, defined as "widely practiced therapeutics with no plausible mechanism,[2]" is an area of great public and scientific interest, as well as of great controversy.[3,4] Although prayer is one of the most ancient of healing practices, the scientific literature studying prayer is still quite young. In this issue of the journal, Benson et al report the sixth and largest prospective, randomized, placebo-controlled study of distant prayer cardiovascular patients[1,5-8] in the STEP.

It is not surprising that so much of the study of healing effects of prayer would be pursued in the "high tech" world of cardiovascular care,[9] as heart disease invariably faces patients, families, and loved ones with the immediate prospect of death, myocardial infarction, and stroke, either from the disease or from the procedures associated with its treatment. In this setting, the cultural practices of patients, families, and medical staff frequently include the personal use of prayer or solicitation of prayer with therapeutic intention from other devotees. Previous trials include 3 studies in coronary care unit populations[5-7] and 2 in percutaneous coronary intervention populations.[1,8] STEP is the first report of distant intercessory prayer in patients undergoing coronary artery bypass surgery.

In the absence of mechanistic insight, attention to the quality of clinical trials science used for the study of an emotionally and culturally charged "therapy" such as intercessory prayer[10] becomes critical to the interpretability of study findings and to the utility of such findings to the practice of medicine. In this regard, the STEP investigators are to be congratulated for reporting a large, prospective multicenter study using classic clinical end points (as defined by the Society of Thoracic Surgeons database), with rigorous quality control in the study's conduct and a thoughtful and rigorous statistical analysis plan including sensitivity analyses for missing data. The STEP study is unequivocally a landmark in the peer review literature on this topic.

A few study design questions can, nonetheless, be raised. "Constraints on how intercessory prayer was provided" excluded all but a handful of prayer groups and may have affected the actual prayers performed by those groups. As the authors point out, although on the one hand this gave rigor to the prayer method used, it may also have impacted the quality of the prayer itself and leaves open questions about the generalizability of the STEP findings relative to other intercessory prayer approaches.

The primary analytic plan also represents some fundamental trade-offs, as is almost always the case in clinical trial planning. As the authors carefully explain, their prospective plan compared Group 1 (prayer but uncertain) versus Group 2 (no prayer but uncertain) and independently compared Group 1 (prayer but uncertain) with Group 3 (prayer and certain). This structure allows a single feature to be assessed for efficacy in each comparison: the effect of adding prayer in a double-blind (Group 1 vs Group 2) and the effect of certainty versus uncertainty in patients receiving intercessory prayer (Group 1 vs Group 3). The trade-offs of adopting this analytic plan, however, especially in light of the data, are relatively unexplored in discussion by the authors, and although rethinking the analysis plan after the data have been examined may be fatally biased, some discussion of the absence of even secondary analyses of all exposure to prayer versus placebo or a 3-way comparison model across the studied groups might have been helpful to readers.

Defining other features of the study cohort might also have been revealing. Patients enrolled in the double-blinded arms might still be inclined to guess or even

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believe they know what their treatment assignment actually was. In elective percutaneous coronary intervention patients enrolled in a double-blinded prayer study, about two thirds of patients not actually assigned prayer believed that they were.[8] In STEP, documentation of what patients were actually assigned versus what they believed they were assigned in Groups 1 and 2 (uncertain prayer and uncertain no prayer, respectively) might have provided insight into the possible role of a placebo effect.

With excellent clinical science, overall, and a handful of design criticisms inevitable in clinical studies, the most striking element of the STEP report is in the interpretation of the study results showing significantly worsened outcomes in one of the experimental arms. While presenting these results clearly and noting them in discussion, the investigators take an almost casual approach toward any explanation, stating only that it "may have been a chance finding." It is rather unusual to attribute a statistically significant result in the primary end point of a prospective, multicenter randomized trial to "chance." In fact, such attribution is antithetical to the very definition of what α error and statistical certainty imply: that the worse outcomes are almost certainly related to the therapy and not the play of chance. If the results had shown benefit rather than harm, would we have read the investigators' conclusion that this effect "may have been a chance finding," with absolutely no other comments, insight, or even speculation?

A more straightforward interpretation might have been that patients who were asked to hide a clinical study treatment assignment from their bedside staff *and* "who were certain that intercessors would pray for them had a higher rate of complications," that is, that this construct appears to do harm. Literally, from the analysis plan, this "harm" is measured relative to the double-blinded prayer cohort (Group 3, prayer and certain vs Group 1, prayer and uncertain), although Group 1 itself had worse absolute rates of complications than the standard care, Group 2 (no prayer, uncertain). Secondary analyses of the data that might help try to understand whether the stress on the patient in the preoperative period was the key detrimental factor or whether it was the intercessory prayer per se that may be unsafe in this patient population were not performed. If space constraints limited the opportunity to present secondary analyses, at least some indication of their potential might have been commented upon.

Compared with the very high level of study design, conduct, and analysis, the STEP investigators' interpretation of the study results appears to reflect more the cultural bias that healing prayer could only seriously be explored for effectiveness, not for safety issues. Culturally, "harm" resulting from prayer is generally ascribed to overtly "negative" prayer, such as hateful prayer, voodoo, spells, or other black magic.[11] Positively intended intercessory prayer is considered a priori to be only capable of doing good, if it does anything at all. But this cultural dichotomy is medically problematic and ethically unacceptable in the setting of a clinical trial performing structured experimentation on human subjects. Particularly in the absence of mechanistic insight, outcome researchers must be vigilant in asking the question of whether a well-intentioned, loving, heartfelt healing prayer might inadvertently harm or kill vulnerable patients in certain circumstances. Although the STEP data do not actually prove that prayer had an untoward effect on coronary artery bypass graft patients, to simply write off significantly worse outcomes in one of the experimental arms as the play of chance is in striking contrast to all the other measures the STEP coordinating center and investigators took to ensure the safety of participating patients and quality of the study data. Thus, although the STEP investigators used every appropriate means of protection of the human subjects who participated in their study, the casual approach to the question of safety in the final data interpretation promotes a dangerously ambiguous message to investigators who might be inclined to do research in this area in the future.

In the study of noetic therapies and, perhaps most particularly, in the study of intercessory prayer, unique issues of personal sensitivity, underlying assumptions on the part of the investigators, and ethical obligations abound.[9] Approaching a patient to participate in a prayer study before a procedure could inadvertently alarm a patient, "You mean I'm so sick that I might need prayer?" Even the assumption that standard clinical outcome measures are appropriate end points for studies of prayer must be carefully examined; for instance, many prayers for the sick contain the implicit objective of easing the passage of the spirit out of the body, an outcome which, by Society of Thoracic Surgeons definition, would be coded as death.

In a randomized single-center study of prayer in coronary care unit patients, Harris et al[6] were supported by the hospital institutional review board (IRB) to conduct the study without obtaining informed consent from patients. The concern leading to this design element was a deep and thoughtful one: patient awareness that a study of prayer was ongoing might profoundly change the spiritual landscape being studied. The IRB was duly consulted, and the study design was approved based on the IRB's conclusion that this therapy "could not possibly do harm." Although for personal or cultural practices assumptions of Divine benevolence may be both relevant and satisfactory, for clinical research, such an assumption could only be considered scientifically naive as in the history of medicine there has never been a healing remedy that was actually effective without having potential side effects or toxicities.

Rigorous thinking is not an indictment of prayer or prayer's potential healing power. Rather, it is respect

for the complex, redundant, and relatively frail aspects of human physiology in the setting of coronary revascularization. In medical school, almost 30 years ago, we were taught to define health as a state of equilibrium and to understand disease as a fundamental disequilibrium. Protocol addition of an influence we do not mechanistically understand into a physiologic or even "mind-body-spirit" disequilibrium such as heart disease obliges open minded clarity in interpreting the results, even if the results are not what we intend or expect. Both ethically and scientifically, this approach should be no different for the clinical study of intercessory prayer than for any other novel therapeutic.

In STEP, the safety of patients and related ethical obligations to study subjects were conducted, like so much of the study methodology, at the very highest level. Informed consent was required, and data and safety monitoring board oversight was provided. The data, on the other hand, proved to be counterintuitive. The assumption imbedded in the analysis plan was that blinded prayer would be effective and unblinded prayer even more effective, with expected complication rates of 50% in the standard care group, 40% in the blinded prayer group, and 30% in the unblinded prayer group—exactly the opposite of what was actually observed. In the interpretation of obviously counterintuitive findings as "what may have been chance," the STEP investigators have allowed cultural presumption to undermine scientific objectivity. Leading researchers such as the STEP team should be underlining the imperative that mechanistically undefined "frontier" therapy research—even well intentioned intercessory prayer—must be scrutinized for safety issues at an equal or even higher level than efficacy measures if medically important and useful knowledge in this arena is to truly step forward.

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