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Review of Randomized Placebo-Controlled Trials

We read the recent review by Sochacki et al.[1] with great interest. The authors' main conclusion is that major orthopaedic trials involving sham surgery have methodologic deficiencies that may invalidate their conclusions. Considering that no rigorous evidence supports the use of interventions included in these trials, we find the authors' conclusions incongruous.

Evidently, no study is perfect. But do the suggested limitations invalidate the results of sham-controlled trials? The assumption that the included interventions provide benefits is based on data from observational studies that lack even the simplest concept in efficacy analysis, a control group. The authors seem to be implying that we are supposed to rely on observational data or expert opinions rather than data from placebo-controlled studies.

One of the criticisms concerns the lack of analysis of genetic markers for placebo effect. This critique is not valid for 2 reasons. First, there is no reason to presume that knowing the "placebo genes" of the trial population is needed to reduce bias. On the contrary, randomization is the best tool we have to avoid such bias since randomization will distribute hidden covariates efficiently. Second, the study of the genetics of the placebo response is in its infancy and should so far be considered basic research.[2] The results have not yet been applied in clinical studies in any field of medicine. Considering the current status of the "placebome" research, it is a gross overstatement to demand the analysis of genetic markers for placebo response in orthopaedic or any other clinical trial.

Another criticism concerns 2 studies performed in Finland. According to the authors, *sisu*, a mystic cultural characteristic defining the resilience of Finns, invalidates the generalizability of the study results. Here the authors refer to 2 articles. The first one is a review describing the potential advantages the Nordic countries have for pioneering in genome-wide association studies.[3] It describes the collaborative initiative called SISu (Sequencing Initiative Suomi [=Finland in Finnish]). Here, SISu is simply an acronym that has nothing to do with sisu, the "*form of courage, grit, and determination*" in Finland. Nowhere in this paper do the authors claim that studies including patients "*born and raised in Finland*" could not be extrapolated to the rest of the world. The second reference is to a short story of an elderly man with metastatic melanoma written by his treating doctor after the patient's death.[4] The man certainly displayed *sisu* during his life, but again, the story provides no justification for the claims made by the authors.

Finally, authors state that "no patients underwent psychiatric or psychologic evaluation to test their competence to participate in a randomized sham surgery trial." They seem to imply that consenting to a potentially harmful surgical procedure that has not been rigorously evaluated does not require psychiatric evaluation but consenting a study evaluating such a procedure does.

Regardless of the presented shortcomings, sham-controlled studies provide the greatest level of evidence we can currently deliver to our patients. While any improvement in methodology should be embraced, the claims made by authors are not supported by their analysis.

Aleksi Reito, M.D., Ph.D., Adjunct Professor
Department of Orthopaedics
Tampere University Hospital
Faculty of Medicine and Health Technology
Tampere University
Tampere, Finland

Teemu Karjalainen, M.D., Ph.D.
Department of Orthopaedics
Traumatology and Hand Surgery
Central Finland Hospital
Jyväskylä, Finland

Pekka Louhiala, Professor
Faculty of Social Sciences
Tampere University
Tampere, Finland

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Author Reply to "Placebo Trials in Orthopaedic Surgery" and "Review of Randomized Placebo-Controlled Trials"

We thank Drs. Harris, Poolman, and Buchbinder[1] and Drs. Reito, Karjalainen, and Louhiala[2] for their interest in and commentary on "Sham Surgery Studies in Orthopaedic Surgery May Just Be A Sham: A Systematic Review of Randomized Placebo-Controlled Trials."[3] We appreciate the opportunity to respond to their comments. As international value-based health care initiatives continue to be rapidly developed and used based on high-quality evidence, we are excited to begin a productive discussion on how to optimize guidelines and policy from sham surgery–controlled investigations in orthopaedic surgery in our reply. We agree with both groups of authors that high-quality sham surgery–controlled randomized studies do have immense value in evidence-based orthopaedic surgery. The intent of our systematic review and the intent of this response are to respectfully characterize the limitations of these studies so that future research may avoid them.

In the quest to achieve the highest-quality evidence-based medicine in orthopaedic surgery, it is fairly safe to assume that we can all agree "the perfect study" does not exist. Despite best efforts of investigators, every study is limited in some way in design, conduct, or reporting. Even the top 10 most-cited randomized trials of all time have significant biases—"all trials inevitably produce bias."[4] Even the seminal placebo surgery–controlled trial in orthopaedic surgery[5] had dozens of significant limitations that "prompted significant criticism from the orthopaedic discipline at large."[6] If we continue to identify and rectify methodologic limitations and bias, the increasing quality can improve the fidelity of the research that we translate to the office and operating room clinical settings. The sham surgery–controlled investigation attempts to mitigate the effect of the surgical placebo response and truly identify whether the actual intervention works (i.e., is it the actual specific effect of the arthroscopic meniscectomy that works, or is it just the placebo effect [and contextual effects] of the knee arthroscopy?). We agree with both the letter to the editor by Harris et al.[1] and the excellent text *Surgery, The Ultimate Placebo* by Harris[7] that there are several reasons that an individual in the placebo group may improve after a treatment or surgical procedure that are not a result of the placebo effect: self-limiting natural history of the condition (Voltaire's "amusing the patient while nature cures the disease"), regression to the mean, concomitant treatment(s), and potentially, other unknown reasons. It is perhaps for these reasons—and not an "actual placebo effect" (which contradicts its definition)—that patients improve after a sham or placebo operation.[8,9] It is for these points that we do owe Harris et al. a debt of gratitude for their efforts in understanding and teaching the surgical and medical communities all there is to know regarding placebo surgery–controlled randomized trials.

The randomized controlled trial (RCT) has always been the ideal investigation to identify whether an intervention works: Is an experimental surgical technique (e.g., knee arthroscopy) "better" when compared with a control group (i.e., superior, noninferior, or equivalent) in ideal (efficacy) or real-world generalizable (effectiveness) settings? In theory, randomization may prove causation. However, in practice, randomization may fail.[10] Causal inference experts continue to insist on a healthy dose of skepticism in interpreting the conclusions of randomized trials—"considering the practical difficulties of conducting an ideal RCT, observational studies have a definite advantage: they interrogate populations at their natural habitats, not in artificial environments choreographed by experimental protocols."[11] Relevant to the latter and more pertinent to randomized sham surgery–controlled trials is the issue of the "no treatment" control group, given that in practicality, in patients with significant pain and dysfunction, it is unlikely they would be willing to just "wait and see" how well they do while the surgery and sham groups evolve through trial completion. It is even possible that eligible trial participants who are told about surgical treatment during the informed consent process but are then allocated to nonsurgical treatment (or even a no-treatment natural-history control group) may then equate any or all symptoms to insufficient care, and this may drive them to drop out or cross over to surgical treatment. Nevertheless, despite these known issues, the practicality of the no-treatment control is outweighed by its necessity to obtain the best answer or outcome possible.

Clearly, we humbly recognize that the issue of randomization is not only imperfect but also incredibly controversial. In 2018, Deaton and Cartwright[12] presented a well-written approach to understanding RCTs. On the basis of their article, 18 letters to the editor or