Letter to the Editor

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Performing and interpreting randomized clinical trials

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To the Editor,

The quality of clinical trials determines their usefulness in evaluating a therapy's effectiveness [1]. Initiatives such as the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network have aimed at improving trial methods, mainly by connecting important stakeholders and by producing guidelines for reporting. For randomized controlled trials, the Consolidated Standards of Reporting Trials (CONSORT) Statement [2, 3] provides researchers with checklists to guide trial design, analysis, and reporting in scientific journals [2, 3]. Such initiatives can help ensure that basic methods are employed, thus enhancing trial rigor and reducing bias, and that key information is reported, allowing readers to critically appraise trials. Many academic journals have made it mandatory to use reporting guidelines and to register trial protocols prior to recruitment to assure research integrity [4]. In this letter, we discuss a trial published in the *Journal of the American Osteopathic Association* in 2020 [5] to illustrate some major considerations in designing, interpreting, and reporting a randomized, placebo-controlled trial of osteopathic manipulative therapy (OMTh) and highlight some possible sources of confusion regarding the interpretation of pilot trials.

Tramontano and colleagues [5] published a pilot randomized, placebo-controlled trial reporting on management of patients with patellofemoral pain syndrome (PFPS) based on an assessment of "somatic dysfunction". Notably, the authors assessed osteopathic interventions in a disorder other than low back pain, and there are several commendable aspects of their placebo control design, which is notoriously difficult for nonpharmacological interventions [6–8]. In particular, the researchers specifically trained practitioners in the application of the "sham" therapy and only enrolled therapy-naïve participants, possibly improving blinding.

The placebo intervention in that trial consisted of "passive touching without joint mobilization in a protocolled order. First, the osteopath […] touched the patient's lumbar spine for 10 min and dorsal spine for 10 min, [then] the patient's shoulders for 10 min, hips for 10 min, and neck, sternum, and chest for 5 min" [5]. We congratulate the authors on using an approach that controlled for nonspecific effects of touch and the therapeutic encounter, but we are concerned that the placebo intervention may lack credibility, as it did not address the symptomatic area, which the authors acknowledged [5]. Further, providing touch for 45 min with apparently no movement may have caused patients and practitioners in the control group to lose interest, possibly undermining blinding and leading to attrition (in fact, five of 40 participants (12.5%) were lost, but the authors did not report from which group). Termed "frustrebo effect," [9] this may be an explanation for the lack of change seen in the control group over time, whereas in most trials, placebo groups improve somewhat [10]. This study's design would have been enhanced by assessing the placebo intervention's credibility, blinding effectiveness, and acceptability to patients and practitioners. Indeed, a pilot trial such as this would have been ideal to ask those questions. With more trust in the placebo control intervention, the trustworthiness of trial results would increase.

We suggest that the authors further consider what they assume to be the "active" (or "specific") component of their therapy and then design the placebo intervention to match

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all the nonspecific factors [11–15]. According to the authors, the active component was the manual diagnosis and treatment of "somatic dysfunction" by means of osteopathic techniques [5]. Based on a mechanistic understanding of the intervention, it would have been possible to provide simple touch to the symptomatic area or some form of tissue movement, possibly enhancing the potential of the placebo intervention to be considered by patients as a true treatment. We recognize, however, that there are currently no clear guidelines on the design of a sham intervention in manual therapies, which is why feasibility testing is so important and why pilot studies have a crucial role in the development of good-quality trials.

According to the authors, their study was a pilot trial, defined as a future study conducted on a smaller scale, distinctly aimed at preparing a larger trial [16–18]. Pilot trials are also valuable for hypothesis-generation and the development and assessment of complex intervention programmes [16] – all of which are important objectives in osteopathy. However, such small trials hold an inherently larger risk of bias, which is why many authors recommend not drawing conclusions regarding efficacy or clinical effectiveness [19, 20]. In doing so, small trials also introduce bias into literature reviews and metaanalyses [21] – a problem endemic to the manual therapy field [22].

Despite calling their study a pilot, there is no indication in their report that Tramontano et al. [5] are planning to conduct such a main study. Instead, the results are interpreted as if they were based on a sufficiently powered and well-designed trial to draw implications regarding the intervention effectiveness: "Significant differences in VAS scores [pain intensity] were found between the [...] groups. These findings emphasize that [osteopathy] can lead to reduced pain in patients with PFPS." [5] Given these circumstances, we suggest that the authors should clarify the aims of the trial, including whether it was in fact a pilot of a planned trial. If so, the focus should have been on reporting the success of the pilot and lessons learned rather than premature judgements about efficacy or effectiveness. If taken to be a full-scale trial, it would have to withstand a formal risk of bias assessment. Without going into detail regarding further methodological shortcomings, but to illustrate that our concerns reflect current research practice, we offer an assessment of the study by Tramontano et al. [5] trial using the Cochrane risk-of-bias tool [23] and a risk-of-bias visualization tool [24] (Figure 1).

In summary, the work by Tramontano et al. [5] has the potential to be developed into a valuable contribution to osteopathic research, especially regarding placebo control methods for a long-term trial of multimodal treatment. In its current form, however, we are concerned that readers unfamiliar with the required methodological standards of clinical trials are misled to believe that the described osteopathic interventions have been demonstrated as effective treatment for patellofemoral syndrome – a conclusion which, as we have shown, cannot be drawn from the present trial. Study authors must clearly describe methodological limitations and report that the focus of pilot and feasibility studies is to enhance the design of appropriately powered and designed studies, which may then make claims about effectiveness and efficacy of interventions. For dedicated research colleagues, we kindly suggest that pilot work and larger scale trials be planned and reported with more attention to accepted research guidance. We further suggest that only trials with preregistered protocols be published to improve the trustworthiness of the analysis [25]. We need a concerted effort to enhance the quality of research and research dissemination to support clinicians and policy makers when considering published evidence.

Editor's Note: *Journal of Osteopathic Medicine* now only accepts for publication prospective human subject studies that have been submitted to a clinical trial registry, in accordance with the Declaration of Helsinki.

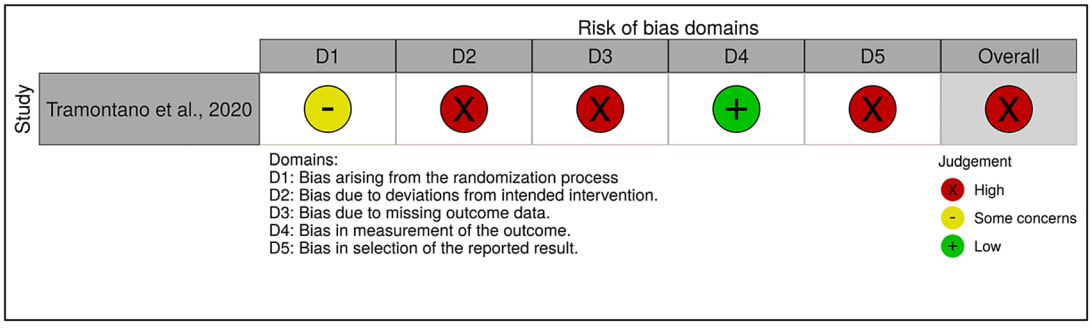

Figure 1: Risk of bias for the outcome "general pain" as measured per patient self-report on a visual analogue scale (VAS) in Tramontano et al [5]. The data was rated by three independent reviewers (D.H.S., J.D.R., J.V.) and reconciled by discussion. Ratings were based on the risk-of-bias tool 2 [23], and the figure was created with the risk-of-bias visualization tool [24].

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