

ORIGINAL ARTICLE

Sample size, study length, and inadequate controls were the most common self-acknowledged limitations in manual therapy trials: A methodological review

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Abstract

Objectives: The aim of this study was to quantify and analyze the presence and type of self-acknowledged limitations (SALs) in a sample of manual therapy (MT) randomized controlled trials.

Study Design and Setting: We randomly selected 120 MT trials. We extracted data related to SALs from the original reports and classified them into 12 categories. After data extraction, specific limitations within each category were identified. A descriptive analysis was performed using frequencies and percentages for qualitative variables.

Results: The number of SALs per trial article ranged from 0 to 8, and more than two-thirds of trials acknowledged at least two different limitations. Despite its small proportion, 9% of trials did not report SALs. The most common limitation declared, in almost half of our sample, related to sample size (47.5%) followed by limitations related to study length and follow-up (33.3%) and inadequate controls (32.5%).

Conclusion: Our results indicate that at least two different limitations are consistently acknowledged in MT trial reports, the most common being those related to sample size, study length, follow-up, and inadequate controls. Analysis of the reasons behind the SALs gives some insights about the main difficulties in conducting research in this field and may help develop strategies to improve future research. © 2020 Elsevier Inc. All rights reserved.

Keywords: Self-acknowledged limitations; Manual therapy; Reporting; Quality; Transparency; Guidelines

Author statement: G.A. conceptualized and designed the study. G.A. and G.U. were responsible to create the first version of the data extraction form and G.A., I.S., M.S., A.F., C.F., and G.U. piloted the form and contributed to reach the final version. I.S. was responsible of the search strategy and articles retrieval. I.S., M.S., A.F., C.F., and G.U. were involved in the data extraction process forming pairs with G.A.. R.N. and G.A. were responsible of data analysis. G.A. provided the first manuscript draft which received critical revision by G.U., I.S., and X.B. All authors read and approved the final manuscript. Gerard Alvarez is a PhD student on Biomedical Research Methodology and Public Health in the Medical Department of the Universitat Autònoma de Barcelona, Barcelona, Spain.

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Key findings

- Over two-thirds of manual therapy trials acknowledged at least two different limitations.
- They are mostly related to sample size, study length and follow-up, and inadequate controls.
- In the 9% of the trials, no limitations are acknowledged.

What this adds to what was known?

- Identifying the most self-acknowledged limitations in a large sample of manual therapy trials provides a better understanding of research-related difficulties in that field.

What is the implication and what should change now?

- Future trials in the field of manual therapy should be designed in a way that these main limitations are overcome.
- We recommend the development of specific guidelines on how to report and acknowledge limitations to enhance research quality and transparency.

1. Introduction

Limitations of a study are features of its design and execution that could have affected the interpretation, validity, and applicability of the findings [1]. As they can never be excluded, authors should always consider acknowledging the potential limitations of their work [2]. In fact, recognition and discussion of potentially important limitations and their likely implications on the interpretation of the findings represent a central part of the scientific discourse. Moreover, such discussion can benefit the scientific community as it allows the investigators of future studies to address these limitations and produce higher quality studies [3].

This notwithstanding, insufficient acknowledgment of limitations in discussion sections has been previously found to be among the most important deficiencies in scientific articles [4]. Some studies have reported a lack of or inappropriate recognition of limitations in the medical literature. A study by Ioannidis, using automated keyword searching, found that only 17% of 400 articles published in leading medical journals used at least one word referring to limitations [5]. Ter Riet et al. analyzed the reporting of limitations and the use of “hedging patterns” (i.e., modal verbs like “may” or “could,” adverbs like “apparently” or “possibly,” and lexical verbs like “suggest [that]” or “believe [that]”) in 300 biomedical

publications published in 30 high- and medium-ranked journals in 2007. They found that 27% of the articles did not report any limitations, and that there were major differences between journals in how uncertainty was expressed and limitations acknowledged. Despite improvement over time, the conclusion was that the reporting of limitations was probably incomplete [6]. Collectively, this literature shows that failing to acknowledge limitations is still a significant problem in the biomedical literature. Proposed strategies to help improve transparency and contribute to the evolving culture of research reproducibility include biomedical text mining to automatically recognize self-acknowledged limitations (SALs) in clinical research publications and “second independent” discussions (the participation of an additional author who is independent to the study and whose role is to identify its limitations) [7–9].

Limitations may be omitted for several reasons. Researchers may feel under pressure to show that their work is important, robust, and limitation-free [5]. Acknowledging limitations may be perceived by authors as a source of negative comments from peer reviewers or even as a motive for nonacceptance by journals [3]. However, there is a compelling argument that articles that fully attempt to address limitations are likely to be widely cited and shape the future research agenda [3,9]. Manuscript length limitations in traditional print journals may be another reason to avoid or be sparse in acknowledging limitations. In fact, the superiority of open-access journals in acknowledging limitations may reflect space availability [5]. The increasing existence of open-access journals and online publishing should be seen as a solution regarding length restrictions.

Manual therapy (MT) is a physical treatment used by a variety of therapists to treat mainly musculoskeletal pain and disability [10]. It includes massage, joint mobilization/manipulation, myofascial release, nerve manipulation, strain/counterstrain, and acupuncture [11]. In the field of physical and MT, although the number of publications has increased significantly in recent years, this does not seem to have been accompanied by improved quality or reporting [12–16]. Because of its nature, research in complex, nonpharmacological interventions is exposed to a number of methodological difficulties that can affect both internal and external validity [17,18], leading to various study limitations [19]. These weaknesses have been previously reported in several publications focused on the quality and reporting of nonpharmacological randomized controlled trials (RCTs) [20–22]. Given this situation, and for the sake of a correct interpretation of the findings, a complete description of SALs should be expected in this kind of literature. However, to the best of our knowledge, no attempts have been made to evaluate this aspect in MT articles.

The aim of this study was to quantify and analyze the presence and type of SALs in a sample of MT RCTs.

2. Methods

2.1. Eligibility criteria

We report a secondary analysis from a previous systematic methodological evaluation of a random sample of 100 MT RCTs published between 2000 and 2015 [15]. While we first focused on reporting, the present study assessed the presence and type of SALs in the sample. For the purposes of the present study, we extended our sample with 20 additional trials published from 2015 to 2020 to assure the validity of the results and to be representative of articles published up to the present day. Criteria for inclusion were that at least one of the interventions (experimental or control) should include some form of MT. A validated search strategy (Appendix 1) was used to retrieve MT articles [23]. More details on eligibility criteria, search strategy, and a description of the reviewers are available elsewhere [15].

2.2. Data extraction

Two researchers, one with expertise in clinical research methodology (GU) and the other one with expertise in the field of MT (GA), defined by consensus, a list of 12 items indicating broad categories of common limitations in conducting clinical trials. We developed a data extraction form including these categories and an additional open field to register any other limitation beyond those defined.

The reviewers (GA, IS, MS, AF, CF, and GU) were first asked to identify any of the limitations defined in the abstract and discussion sections from the trial reports and then to transcribe the information related to the SALs identified. We extracted data in pairs of independent reviewers.

2.3. Data analysis

From the data extracted, we accounted for the trials disclosing the predefined limitations. Two reviewers (GA and RN) compared iteratively the limitations descriptions reported in the trial reports to obtain common themes and define specific limitations implementing a thematic analysis [24]. Descriptive analyses were performed using SPSS version 22.0 (IBM Corporation, Armonk, NY), using frequencies and percentages of qualitative variables, including the 95% confidence interval.

3. Results

3.1. Description of articles

The 120 trials analyzed assessed the impact of six different modalities of manual therapies (soft tissue techniques (29%), spinal manipulation therapy (23%), joint mobilization (21%), chiropractic treatments (12%), acupressure/reflexology (10%), and osteopathic manipulative treatment (5%)) comparing them with up to 20

different types of control treatments/interventions. In some studies, more than one control intervention was used, and “usual care” (21%), sham interventions (19%), and exercise (18%) were the most common. The trials included a mean of 111 participants (SD = 187). The most frequent studies evaluated physiological responses on healthy or asymptomatic subjects, and the most frequent health problems assessed were lower back pain and neck pain. Thirty-nine percent of the articles reported long-term follow-up. We reported a full description of the articles included elsewhere [15].

The articles studied were published in journals that ranged from 0.12 to 4.63 in the scientific journal ranking (Scimago). At the year of publication, 74% of them were first quartile journals, 20% were second quartile, and 6% were third quartile [25].

3.2. Number of limitations

Initially, a list of 53 specific limitations was identified, and after discussion between reviewers to establish a clear definition of each specific limitation, a final list of 39 was reached (Table 1). Limitations were located almost exclusively in the discussion section. Only two articles (1.6%) included a specific limitation section in the Abstract. The number of SALs per article ranged from 0 to 8, and 80% of the articles acknowledged at least 2 different limitations. In 9% of the articles, no SALs were found (Fig. 1).

3.3. Categories and specific limitations reported

Table 2 shows the frequency and categories of SALs reported in the articles. The most common limitation declared, in almost half of our sample, related to sample size (47.5%), followed by limitations related to study length and follow-up (33.3%) and inadequate controls (32.5%). Limitations regarding funding or the selected centers and/or care providers were the least reported. For each category of limitations, several explanations were given by the authors, and in some cases, they reported different study weaknesses leading to the same type of specific limitation. Table 2 shows the frequency of these explanations, which allow better understanding of the specific limitations within each category. For example, regarding sample size limitations, in 87.7% of the articles, authors declared a lack of statistical power to provide reliable results, while just 8.8% declared recruitment difficulties.

4. Discussion

In the present study, we quantified and analyzed SALs in a sample of 120 manual therapy trials. While previous research assessing SALs has focused on high-impact journals regardless the study field [5,6], we extended our focus to trials published in any journal to capture the breadth of this kind of clinical research in manual therapy. Overall,

Table 1. Type of limitations and reasons reported by authors

Category 1—randomization and/or concealment	
Unbalanced groups	After randomization, the number of subjects allocated to each group was unequal.
Lack of stratification	Randomization method did not include stratification.
Selection bias not excluded	Randomization methods were not the most recommended (e.g., ballot boxes) or allocation was not concealed.
Category 2—Blinding	
Statistician blinding	People performing the statistical analysis were not blinded.
Outcome assessor blinding	People in charge of data collection were not blinded.
Patient blinding	Patients were not blinded with respect to the study groups.
Care provider blinding	People providing the interventions were not blinded with respect to the study groups.
Category 3—Lost to follow-up/dropouts	
Unbalanced dropouts	Dropout rate between study groups was unequal.
Many lost to follow-up	Discontinuation rate was superior than expected/estimated leading to underpowered studies and less precise results.
Category 4—Sample size	
Unpowered study	Inability to detect differences between groups due to sample size.
Convenience sampling	The sampling method was linked to specific study needs.
Recruitment less than expected	The sample size did not reach the estimated number due to recruitment difficulties.
Category 5—Inadequate control	
Active control	An active intervention (e.g., exercise or usual care) was selected as control.
Simulation (sham) not optimal	Some effects related to sham interventions could not be ruled out.
Different parameters between groups	The dosage, the number of sessions, or their duration was different in the control group.
Different baseline parameters.	Comparison of baseline data showed significant differences in the control group
Category 6—Funding	
Limited funding	The limited or lack of funding affected the study progress or completion.
Category 7—Type of setting/care provider/s	
Unicentric	Study was conducted recruiting participants from a single center.
Number of care providers	Intervention delivered by a single investigator.
Category 8—Inadequate subjects	
Asymptomatic subjects	Leading to a limited clinical interpretation of the results.
Diagnostic criteria	Lack of standardized diagnostic criteria to include participants.
Very specific population	Inclusion criteria considered too restricted. (e.g., single gender, athletes only, education level, or race).
Category 9—Study length and follow-up	
No long-term follow-up	Only short-term effect was evaluated.
Missing data due to study length	Dropouts or losses to follow-up derived from a very long follow-up time.
Unequal follow-up	Follow-up between the study groups was different.
Category 10—Intervention	
Additive effects	It was not possible to know the net effect of every component in multimodal treatments.
Limited treatment area	The intervention was applied to a very specific body region (e.g., single joint or vertebral segment).
Treatment parameters not standardized	Specific parameters of manual techniques were not standardized (e.g., amount of force, direction, or speed).
Lack of individualization	A treatment protocol was applied without adapting the interventions to the characteristics of the individuals or to the diagnostic criteria.
Therapist profile	Care providers required specific training on the intervention, or care providers had different previous experience

(Continued)

Table 1. Continued

Category 11—Outcome measures	
Reliability of the measurement	Lack or low reliability of outcome measures (e.g., self-reported results).
Lack of measurement data	Some relevant data were not collected during the study (e.g., demographics or clinical variables that would potentially provide interesting findings).
Measurement sensitivity	Outcome measures were not sensitive enough to detect subtle changes (e.g., use of ordinal scales).
Validity of the measurement	The selected assessment instrument was not originally validated for that specific population.
Suboptimal statistical analysis	Findings were not adjusted for covariates.
Category 12—Compromised generalization of the results (This category includes those self-acknowledged limitations that were mentioned specifically in regards to their impact on the generalization of the results or external validity.)	
Compromised generalization due to type of setting.	The characteristics of the setting where the study was conducted limited the generalization of the results
Compromised generalization due to specific population	The subjects' characteristics of the sample limited the generalization of the results.
Compromised generalization due to measurement	The measurement instrument selected to assess the effect of the intervention sample limited the generalization of the results.
Compromised generalization due to intervention	The type of intervention or the way it was delivered limited the generalization of the results.

our results indicate that at least two different limitations are consistently acknowledged in MT reports. Furthermore, the analysis of the arguments reported by authors provide some explanation to help understand the specific difficulties that MT investigators face and in turn establish strategies, recommendations, or guidelines to improve these. The following discussion focuses on those SALs present in at least 20% of our sample.

4.1. Limitations related to sample size

The most reported SAL related to sample size (47.5%) and, within this category, the main reason given by the authors was that the studies lacked statistical power to detect effect differences between groups (87.7%). In general, RCTs in MT frequently involve small sample sizes [26]. Research in MT is often conducted in private centers and outpatient services which limits recruitment possibilities, leading to underpowered studies. For example, in our sample, although

pilot studies were not excluded ($n = 15$), only 31% of the RCTs had samples greater than 100 participants [15].

It has been found that sample size is related to an a priori sample size calculation: trials that perform an a priori sample size calculation have considerably larger median sample sizes than those that do not [27]. However, despite improvement over time, reporting of sample size calculation and power analysis remains inadequate regardless the study type [28]. In the field of rehabilitation trials, in a sample of 222 RCTs, Castellini et al. found that only 36% reported sample size calculations [29]. In the same line, Gonzalez et al. concluded that just 34% of the physical therapy trials relevant to musculoskeletal conditions reported adequate sample size calculation [14]. In our sample, a description of sample size calculation was found in 49% of the articles. Therefore, a statement of sample size calculation should be seen as a key requirement for MT investigators.

While adequate sample size is desirable, some authors have argued that underpowered trials might be acceptable if investigators use methodological rigor to eliminate bias, report properly to avoid misinterpretation, and always publish results to avoid publication bias [30]. According to Schulz et al., readers should be more concerned about systematic errors rather than inadequate sample size. In fact, sample size deals more with the precision of the estimation of effect and not necessarily with the validity of the study [26]. The power of the trial is expressed in the confidence interval. Hence, if methodological issues are carefully considered, the power is no longer a major concern [30]. In turn, validity can dramatically influence the effect size.

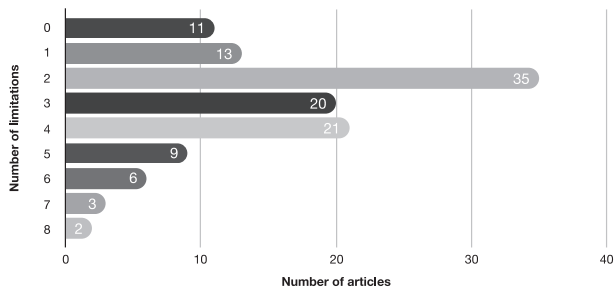


Fig. 1. Number of limitations reported in the articles (n = 120).

For example, in the field of low back pain, studies with higher risk of bias reported effect sizes that were, on average, 50% greater than the estimates reported in trials with a lower risk of bias [31]. In a sample of trials evaluating treatments for hip and knee osteoarthritis, it has been shown that inadequate random sequence generation and lack of allocation concealment and double-blinding yielded larger treatment effects [20].

4.2. Limitations related to inadequate control intervention

In the field of physical, manual, and rehabilitation medicine, the lack of high-quality clinical research can be partially explained by the inherent difficulty in conducting double-blinded placebo-controlled clinical trials [32,33]. In our sample, limitations related to inadequate control intervention were reported in 32.5% of the reviewed articles. Within this category, the main reason stated by authors (41%) pointed to placebo or sham interventions not being optimal for the comparison. In the field of MT (or any discipline with a high interaction between patients and care providers), the use of placebos or sham interventions is highly influenced by the therapist who delivers the treatment [26,33]. Thus, in manual sham RCTs, isolating the “active ingredient” from other effects can be very complex [34]. However, key authors in the field of MT conceptualize placebo as an active and important mechanism in MTs [35], including the placebo response as an inseparable and “always present” mechanism of MT effect [36,37].

Therefore, recommendations for future research should include both improvements in placebo/sham procedures and strategies to better assess and report the placebo response in both the intervention and the control group. By using appropriate placebos, it is possible to minimize several kinds of bias in RCTs and to improve research quality. However, there is still a lack of a common, valid manual placebo gold-standard [34]. Moreover, although methodological recommendations have been made by authors in the field of rehabilitation and MTs [32,38,39] and the Consolidated Standards of Reporting Trials (CONSORT) and other statements provide guidelines to report control interventions, there are no clear, unified guidelines on the design or description of sham/placebo procedures [21,40]. Within this scenario, we emphasize once more the importance of complete reporting. For example, in a review of 64 studies in the field of osteopathy, Cerritelli et al. found that trials systematically underreported details on sham procedures, sham dosage, and sham operator. These findings, alongside the high heterogeneity and within-study variability between sham and real treatment procedures profoundly compromise study validity [34]. Fortunately, an extension of the Template for Intervention Description and Replication (TIDieR) for placebo-controlled trials (TIDieR–Placebo) is currently registered in the EQUATOR Network as a guideline under development [41], which is

expected to be a useful tool to facilitate the design of better research in the field.

4.3. Limitations related to blinding

Control-related limitations are linked to blinding strategies, which, in our sample, accounted for 28.3% of all SALs (Table 2). In fact, when comparing clinical trials evaluating nonpharmacological vs. pharmacological treatments, lack of blinding in nonpharmacological treatment articles explained most of the methodological differences [20]. In the field of physical medicine and rehabilitation, reporting of blinding still does not follow current recommendations [42]. Despite the recent controversies raised on the role of the impact of blinding on effect estimates in randomized trials [43], in that particular field, lower reporting of blinding among trials with positive outcomes have been reported [42]. Blinding is less frequently reported in RCTs assessing nonpharmacological interventions, possibly due to the difficulty in achieving and maintaining it [21]. While blinding outcome assessor(s) should be feasible in most cases, blinding patients is challenging and almost impossible for manual therapists. Addressing this issue specifically, Boutron et al. published in 2007 a list of blinding methods used in nonpharmacological trials and provided guidelines to overcome some related difficulties [21]. Among other possible strategies, they proposed blinding participants to study hypotheses (modified Zelen design) and the use of attention-control interventions or placebo control interventions that are not identical to the active treatment [21]. The strengths and limitations of each method should be carefully considered in every case. In the other hand, trials with subjective outcomes, complex or operator-dependent interventions such as MTs could more easily be biased by beliefs and expectations [44]. The strength and direction of preconceived beliefs likely modifies the effect of blinding [44], and contextual factors effects are well documented in MT literature [45–47]. In this scenario, measuring credibility of the treatment, participants' expectations or registering participants' preferences at the beginning of the trial before randomization could help to assess the strength of the treatment [21]. Finally, blinding is rarely tested, and there is methodological uncertainty on how to assess it [48]. Although a test of blinding success might be seen as a good standard practice to adopt, difficulties to assess its impact on potential bias have been reported [49,50]. On the contrary, pretrial assessment of blinding procedures and explicit reporting of who was blinded and by what means is strongly recommended [51].

4.4. Limitations related to study length and follow-up

Study length and follow-up is another common limitation in MT trials (33.3% in our sample). The main study length limitations declared related to the lack of a long-term follow-up (87.5%). Collectively, the literature on specific

Table 2. Frequency and type of reported limitations

C1	Randomization and/or concealment	N articles	Frequency [CI 95%]
<i>N</i> = 13/10.8% [5.9 to 17.8]	Unbalanced groups	2	15.4% [1.9 to 45.4]
	Lack of stratification	3	23.1% [5.1 to 53.8]
	Selection bias not excluded	8	61.5% [31.5 to 86.1]
C2	Blinding	N articles	Frequency [CI 95%]
<i>N</i> = 34/28.3% [20.5 to 37.3]	Statistician blinding	1	2.9% [0.1 to 15.3]
	Outcome assessor blinding	4	11.8% [3.3 to 27.5]
	Patient blinding	24	70.6% [52.5 to 84.9]
	Care provider blinding	17	50.0% [32.4 to 67.6]
C3	Lost to follow-up/dropouts	N articles	Frequency [CI 95%]
<i>N</i> = 18/15% [9.1 to 22.7]	Unbalanced dropouts	1	5.6% [0.1 to 2.67]
	Many lost to follow-up	17	94.4% [72.7 to 99.9]
C4	Sample size	N articles	Frequency [CI 95%]
<i>N</i> = 57/47.5% [38.3 to 56.8]	Unpowered study	50	87.7% [76.3 to 94.9]
	Convenience sampling	2	3.5% [0.4 to 12.1]
	Recruitment less than expected	5	8.8 [2.9 to 19.3]
C5	Inadequate control	N articles	Frequency [CI 95%]
<i>N</i> = 39/32.5% [24.2 to 41.7]	Active control.	14	35.9% [21.2 to 52.8]
	Simulation (sham) not optimal	16	41% [25.5 to 57.9]
	Different parameters between groups	4	10.3% [2.9 to 24.2]
	Different baseline parameters	5	12.8% [4.3 to 27.4]
C6	Funding	N articles	Frequency [CI 95%]
<i>N</i> = 5/4.2% [1.4 to 9.5]	Limited funding	5	100% [47.8 to 100]
C7	Type of setting/care providers	N articles	Frequency [CI 95%]
<i>N</i> = 9/7.5% [3.5 to 13.8]	Unicentric	8	88.9% [51.7 to 99.7]
	Number of care providers	1	11.1% [0.3 to 48.2]
C8	Inadequate subjects	N articles	Frequency [CI 95%]
<i>N</i> = 31/25.8% [18.3 to 34.6]	Asymptomatic subjects	4	12.9% [3.6 to 29.8]
	Diagnostic criteria	5	16.1% [5.4 to 33.7]
	Very specific population	23	74.2% [55.4 to 88.1]
C9	Study length and follow-up	N articles	Frequency [CI 95%]
<i>N</i> = 40/33.3% [25.0 to 42.5]	No long-term follow-up	35	87.5% [73.1 to 95.8]
	Missing data due to study length	2	5% [0.6 to 16.9]
	Unequal follow-up	3	7.5% [1.5 to 20.4]
C10	Intervention	N articles	Frequency [CI 95%]
<i>N</i> = 33/27.5% [19.7 to 36.4]	Additive effects	6	18.2% [6.9 to 35.5]
	Limited treatment area	8	24.2% [11.1 to 42.3]
	Treatment parameters not standardized	17	51.5% [33.5 to 69.2]
	Lack of individualization	5	15.2% [5.1 to 31.9]
	Therapist profile	1	3% [0.1 to 15.8]
C11	Outcome measures	N articles	Frequency [CI 95%]
<i>N</i> = 35/29.2% [21.2 to 38.2]	Reliability of the measurement	9	25.7% [12.5 to 43.3]
	Lack of measurement data	12	34.3% [19.1 to 52.2]
	Measurement sensitivity	2	5.7% [0.7 to 19.2]
	Validity of the measurement	11	31.4% [16.9 to 49.3]
	Suboptimal statistical analysis	4	11.4% [3.2 to 26.7]
C12	Compromised generalization (CG) of the results (<i>n</i> = 26)	N articles	Frequency [CI 95%]
<i>N</i> = 26/21.7% [14.7 to 30.1]	CG due to type of setting	3	11.5% [2.4 to 30.2]
	CG due to specific population	16	61.5% [40.5 to 79.8]
	CG due to measurement	2	7.7% [0.9 to 25.1]
	CG due to intervention	5	19.2% [6.5 to 39.4]

95% confidence interval (CI).

Note: Some articles reported more than one reason (specific limitations) within the same category.

mechanisms of MT concludes that the main effects are short term [36,37]. However, in clinical practice, MT is commonly used to treat chronic conditions [45,52] through therapeutic packages that can last several weeks or months. Therefore, long-term follow-up should be encouraged in MT clinical trials assessing chronic conditions. Ideally, MT investigators should develop intervention models that match the natural history of common problems, considering the trajectory of the symptoms over time as an outcome rather than focusing on specified follow-up time points alone [53].

4.5. Limitations related to inadequate subject selection

Inadequate subject selection appeared as a SAL in 25.8% of our sample and can be linked to limited generalization (21.7%). In both cases, the main reason behind these limitations was the recruitment of a very specific population (Table 2). In a considerable number of cases, asymptomatic subjects were recruited to evaluate the effect of manual interventions on physiological parameters, which may differ in a broader population of patients in a more real-world setting. In other cases, strict inclusion criteria were established, limiting the generalization of the results. As complex, nonpharmacological, person-centered interventions, MTs are delivered as part of a care package rather than as a single treatment [54]. In addition, at least in the field of musculoskeletal problems, patients typically have multiple comorbidities [55–57]. Therefore, a pragmatic attitude should be adopted in MT trials, to try to include little or no participant selection beyond the clinical indication of interest [58]. However, to reach internal validity standards and allow replication, MT trialists might be forced to highly select the sample, compromising the generalization of the results.

4.6. Limitations related to the intervention

Limitations related to the intervention were acknowledged in 27.5% of our sample. The main reason given by the authors was the lack of a standardized protocol (51.5%), which contrasts with the lack of individualization also reported as a specific limitation in 15.2% of this category. Furthermore, whether the treatment has to be applied in a certain localized body region or with a whole-body perspective can also be problematic. In our sample, 24.2% of intervention-related SALs were explained by the treatment being delivered to only a certain area of the body. This reflects again the struggle that MT researchers have in finding the balance between real clinical practice and high-standard methodological requirements or, in other words, between reproducibility and clinical replicability [59]. This aspect is still an open debate that hinders the design and reporting of some interventions. The reporting of nonpharmacological interventions is poor and incomplete [22], and that includes all fields of physical therapy interventions [60] and specifically MT [13,15]. However, beyond the reporting, there is a need to recognize the

particularities of patient-centered touch-based interventions and strike a balance between internal and external validity. Some of the most recent reporting guidelines (e.g., the updated CONSORT extension for nonpharmacological interventions (CONOSRTnpt) [61] or the TIDieR) [22] already include items related to the tailoring of interventions. However, recent research shows that despite the existence of such guidelines, clinical reproducibility is compromised particularly for complex interventions and, as we proposed in a previous publication [15], there is a need for field-specific checklists [59]. Examples of this are the specific reporting guidelines on spinal manipulative therapy [62] and therapeutic exercise [63].

4.7. Limitations related to outcome measures

Finally, SALs related to outcome measures accounted for 29.2% of the limitations reported in our sample. Among the reasons given by the authors, the lack of measurement data and the validity of measurements were the most frequent (34.3% and 31.4%). The selection of valid and meaningful outcome measures is crucial to make research informative to clinical practice, and the outcome measurement tools used in research may not always be the most appropriate in clinical settings [64]. Furthermore, difficulties caused by heterogeneity in outcome measurements are constantly reported in systematic reviews [65] and constitute a challenge in meta-analysis of physical therapy interventions [66]. The use of a standardized set of outcome measures for a given condition (which include different types of outcomes) would be a potential solution to these issues. The Core Outcome Measures in Effectiveness Trials initiative (<http://www.comet-initiative.org>) represents a very useful tool for MT investigators. As an additional recommendation, the use of patient-reported outcomes measures (PROMs) would be a suitable option for patient-centered interventions such as MT. In fact, PROMs are increasingly collected in physiotherapy research and can also be used in clinical settings [67]. A specific CONSORT extension focused on PROMs [68] provides guidelines to researchers to ensure optimal reporting.

4.8. Comment on reported limitations

In the previous sections, we have quantified and described those SALs identified in our sample. However, beyond the descriptive purposes of the present study, this issue deserves further comment to discuss SALs nature, their implications, and impact. Although reported in a different proportion, we could differentiate some SALs with a greater impact on the internal trial validity from others not directly linked to the study design or that reflected issues related to its conducting. Within the first group, eight trials acknowledged potential selection bias due to inconsistencies in the randomization/concealment process, three trials acknowledged unequal follow-up between groups, and four acknowledged suboptimal statistical

analysis. In the second group, we identified SALs that were not truly methodological (e.g., limited funding in five trials) or reported problems derived from the trial progress (e.g., unbalanced groups in two trials) which should be amendable with a rigorous and accurate data analysis.

In accordance with its nature, SALs can have an impact either on the confidence of the trial's effect estimates or to its conclusions, and this could have some implications to practice. Researchers should ensure the acknowledgment of at least those limitations that might entail threats to the study validity when preparing the manuscripts to report the findings of the trial. On the other hand, reporting guidelines should include more specific guidance to improve the accuracy in reporting limitations, defining some mandatory or those highly recommended to report. Journals also should facilitate tools to appraise this issue and its implications during the peer review process.

4.9. Study limitations

We acknowledge several limitations in our study. First, although we selected 20 additional trials to update our original sample with RCTs published between 2015 and 2020, most recent articles might be slightly underrepresented. Second, the categorization of the 12 broad SALs and the list of specific limitations within each category was subjectively established by three members of the research team (GA, GU, and RN). To minimize potential bias in this categorization and to have common criteria for the allocation of every specific limitation to its category, several meetings took place at the beginning of and during the process. Discrepancies were solved through discussion.

5. Conclusion

Recognition and discussion of all potentially important limitations of a study represent a crucial part of the scientific discourse. Our results indicate that at least two different limitations are consistently acknowledged in MT studies, and that those related to sample size, study length and follow-up, and inadequate controls were the most commonly reported. Besides the items already included in reporting guidelines, specific extensions on how to report and acknowledge limitations could potentially enhance research quality and transparency. Furthermore, researchers should be encouraged to report those limitations that could entail a threat to their studies validity. Systematic analysis of the reasons behind the SALs provides some insights on the main difficulties in conducting studies in this field and may prove helpful in the development of strategies to improve future research.

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Supplementary data

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