Intention-to-treat analysis: Are we managing dropouts and missing data properly in research on orthodontic treatment? A systematic review

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Introduction: Intention-to-treat (ITT) analysis is an approach to managing dropouts and missing data in randomized controlled trials (RCTs). In this study, we systematically reviewed orthodontic RCTs to assess the frequency that an ITT analysis was carried out, to compare the number of trials that reported using ITT analyses with those that had truly used it, and to evaluate how dropouts and missing data were managed. **Methods:** Systematic searches were conducted in electronic databases including Cochrane Oral Health's Trials Register (searched on November 30, 2016) and Cochrane Central Register of Controlled Trials (2016) in the Cochrane Library (searched on November 30, 2016), with no restrictions on language, publication year, or publication status. RCTs comparing orthodontic or orthopedic treatments, or comparing orthodontic or orthopedic treatment with a control group without intervention were included. A customized data collection form was created, piloted, and used to gather information from the selected studies. The data extraction was performed by 2 authors independently and in duplicate, with disagreements resolved by discussion with the third author. The studies were assessed for attrition bias. The data were grouped and classified according to 2 categorical variables: sample analyzed and missing data strategy. The results were reported in percentages and descriptively. **Results:** From the 55 RCTs identified, 6 reported using an ITT approach. From these, only 1 study carried out a true ITT analysis (2%). From the 49 RCTs that did not report using an ITT analysis, 12 had used it (22%). The most used method of analyzing missing data was "completer sample" with 19 studies using this method (28%). "Full random sample" and "sufficient dose" were similar, with 13 and 11 studies, respectively (16% and 14%). The most frequently used missing data strategy for studies that did not conduct a true ITT analysis was "sample followed" with 30 studies (81%). For the studies that conducted a true ITT analysis, the most observed missing data strategy was "no dropouts" with 11 studies (79%). **Conclusions:** Less than a third of the RCTs in orthodontics used an ITT analysis. There is a potential lack of understanding on dropouts and missing data management in research on orthodontic treatment. (Am J Orthod Dentofacial Orthop 2019;155:19-27)

One primary purpose of health care research is to identify the best evidence to reduce the uncertainty in clinical decisions. As a result, we need to minimize bias by using excellent study designs. It is established that randomized controlled trials (RCTs) are the gold standard for evaluating efficiency and safety of intervention[1] because a well-designed trial reports outcomes that can be attributed mainly to the type of treatment, instead of preexisting conditions in the treatment or control group.[2]

However, minimization of bias is achieved only when the full sample of participants is analyzed. When there is a loss of participants or data at random, this affects precision. Additionally, if participants are lost or the protocol deviates when patients switch treatment arms or data are missing, this leads to postrandomization bias, as attrition bias. As a result, the potential benefits of randomization can be lost due to inequality between

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the groups, with a consequent incorrect interpretation of the results.[3]

One recommended approach to deal with this problem is the intention-to-treat analysis (ITT).[4] In this approach, data from every subject in the trial are included in the data analysis, regardless of compliance, deviation from the treatment protocol, withdrawal, or any other event after randomization.[5-8] Thus, ITT preserves the aims of randomization and maintains statistical power, since the baseline balance in known and unknown factors is preserved in the average, and the randomized sample is retained.[9]

Another method that is also used as an analytic strategy is the "per-protocol" (PP) analysis.[10] This method involves exclusion of participants who did not meet the inclusion or exclusion criteria or deviated from the protocol (nonadherents). Examples of PP analyses are "sufficient dose," "completer sample," and "false inclusion." In "sufficient dose," the analysis is conducted for only participants who completed a specified amount of treatment or who received at least a minimum dose of medication or treatment. In "completer sample," the analysis is conducted for only patients who completed the medication or treatment phase. In "false inclusion," the participants did not meet the inclusion criteria and were removed from the analysis after randomization.[11,12]

PP analysis has the advantage of simplicity. However, it can only be used when the trial aims to analyze the effects of an intervention on the participants who adhered to the treatment protocol.[13]

PP analysis has often been mistaken for another analytic strategy, the complete case analysis.[12] Different from PP analysis, complete case analysis restricts the analysis to participants who completed the trial, irrespective of their adherence to the protocol.[13]

There is also the "as-treated analysis" that analyzes the participants for the treatment they actually received.[14] This approach has been mainly advocated for the analysis of treatment toxicity.

The investigators must follow a strategy to manage any missing data. There are several approaches: (1) no dropouts, when all participants remain in the study; (2) all followed, with assessments of all participants including dropouts; (3) imputation and its variations: simple imputation (replacement of missing data with 1 estimated value), multiple imputation (replacement of each missing value with a plausible value that is analyzed with standard procedures for complete data and combining the results from these analyses, missing or failure which classifies the missing data as treatment failure, and last observation carried forward which replaces missing final outcomes with the last observed outcome; (4) statistical modeling, selection or pattern-mixture model or shared parameter; (5) sensitivity analysis, repetition of the primary analysis or meta-analysis, substituting alternative decisions or ranges of values for decisions that were unjustified or unclear; (6) subgroup analysis, comparing the baseline characteristics or outcomes between completers and dropouts, since it is tempting to compare effect estimates in different subgroups by considering the meta-analysis results from each subgroup separately; and (7) sample followed, when the analysis is restricted to participants who remained in the study.

In the orthodontic literature, we routinely find it challenging to identify the methods followed by the authors to deal with dropouts and missing data.[11,15] This difficulty was rep orted in a recent review of ITT analysis of 137 orthodontic trials.[16] The authors concluded that most trials misapplied the ITT analysis. As a result, the authors overestimated the results or had a reduced sample size. This study was a broad evaluation of orthodontic trials from 2013 through 2017 and included trials that tended to report the proximal outcome—eg, bonding failure rate. As a result, we are not aware of the extent of this problem in trials that report clinical outcomes and are included in high-level systematic reviews.

Objectives

In this study, we aimed to review clinical orthodontic RCTs included in Cochrane systematic reviews to (1) examine the frequency of ITT analysis in the trials, (2) compare the number of these trials that reported using ITT analyses with those that genuinely conducted it, and (3) examine how dropouts and missing data were managed.

MATERIAL AND METHODS

Protocol and registration

We registered the protocol for this review on the international prospective register of systematic reviews (PROSPERO) from the National Institute for Health Research database (www.crd.york.ac.uk/prospero; protocol number CRD42017076122).

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The study was not funded.

Eligibility criteria

Our selection criteria were the following.

1. Study design: RCTs on orthodontics included in Cochrane Systematic Reviews.

2. Participants: patients who had orthodontic treatment.
3. Intervention: any orthodontic or orthopedic treatment in the intervention group. The control groups were any other type of orthodontic or orthopedic treatment or a control group without treatment.
4. Exclusion criteria: systematic review protocols, neglected systematic review protocols, neglected systematic reviews, inactive systematic reviews, translations, systematic reviews with no inclusion of RCTs, and systematic reviews that were not related to an orthodontic treatment intervention: eg, studies that evaluated bonding, types of bracket, different wires and ligatures, and pharmacologic and nonpharmacologic methods for pain relief.
5. Outcome measures: sample analyzed and missing data strategy.

Summary measures, approach to synthesis, and analysis

We grouped and classified the data according to 2 categorical variables: sample analyzed and missing data strategy.[11] The categories of sample analyzed were the following.

1. Full random sample: the analyses involved the total randomized numbers (with or without imputation or proper statistical modeling that preserved the randomized sample).
2. Random sample followed: attempted (without success) to follow all randomized participants regardless of the amount of medication or treatment completed and conducted analyses on this sample.
3. Sufficient dose: analyses conducted for only participants who completed a specified amount of treatment or received at least a minimum dose of medication or treatment. Participants were included even with poor compliance, absences, broken appliances, or poor hygiene.
4. Completer sample: analyses conducted for only participants who completed the medication or treatment phase. The other participants could be excluded or lost to follow up. They were excluded because of poor compliance, absences, broken appliances, poor hygiene, or low-quality radiographic or photographic records, or when they did not want to wait for the active treatment when allocated to a control group, did not want to use the allocated appliance, did not sign the consent, refused to have impressions taken, or had allergies. Patients were lost to follow up when there were issues such as moving to another place or when they quit the treatment.
5. False inclusion: after randomization, participants did not meet the inclusion criteria and were subsequently removed from the analyses.
6. Unclear: insufficient information was provided to determine the sample analyzed.

We decided that true ITT analyses were those conducted on the full random sample.

When the sample analyzed was "unclear," we considered the study unknown regarding a true ITT analysis.

The categories for the "missing data strategy" variable were the following.

1. No dropouts: no dropouts from treatment, and 100% of the participants were reassessed.
2. All followed: there were dropouts from treatment, but all participants, including dropouts, were reassessed using imputation or statistical modeling to preserve the randomized sample.
3. Imputation and its variations: (a) simple imputation, replacement of missing data using 1 estimated value; (b) multiple imputation, replacement of each missing value with a plausible value analyzed with standard procedures for complete data and combining the results from these analyses; (c) last observation carried forward, using the imputation strategy of last observation carried forward; (d) failure assumed for missing data, assuming that missing data reflected poor outcome (eg, relapse).
4. Sample followed: analyses with data for participants that the researchers could follow or reassess.
5. Unclear: no or unclear information provided.

In addition to this, we selected the trials that stated the conduction of an ITT analysis, as well as those that did not state it.

Information sources, search strategy, and study selection

For this, we used "Archie," the Internet-based repository for Cochrane's documents and contact details.[17] The search terms were orthodontic, orthodontics, orthodontic treatment, dentofacial orthopedics, functional appliances, and oral appliances. Systematic searches were conducted in the following databases for RCTs and controlled clinical trials. There were no restrictions on language, publication year, or publication status: Cochrane Oral Health's Trials Register (searched on November 30, 2016) and Cochrane Central Register of Controlled Trials (2016) in the Cochrane Library (searched on November 30, 2016). All studies were peer reviewed regarding the inclusion criteria for each variable and each category by 2 evaluators (K.B.S.L.B. and B.T.). In case of discrepancies, a third evaluator

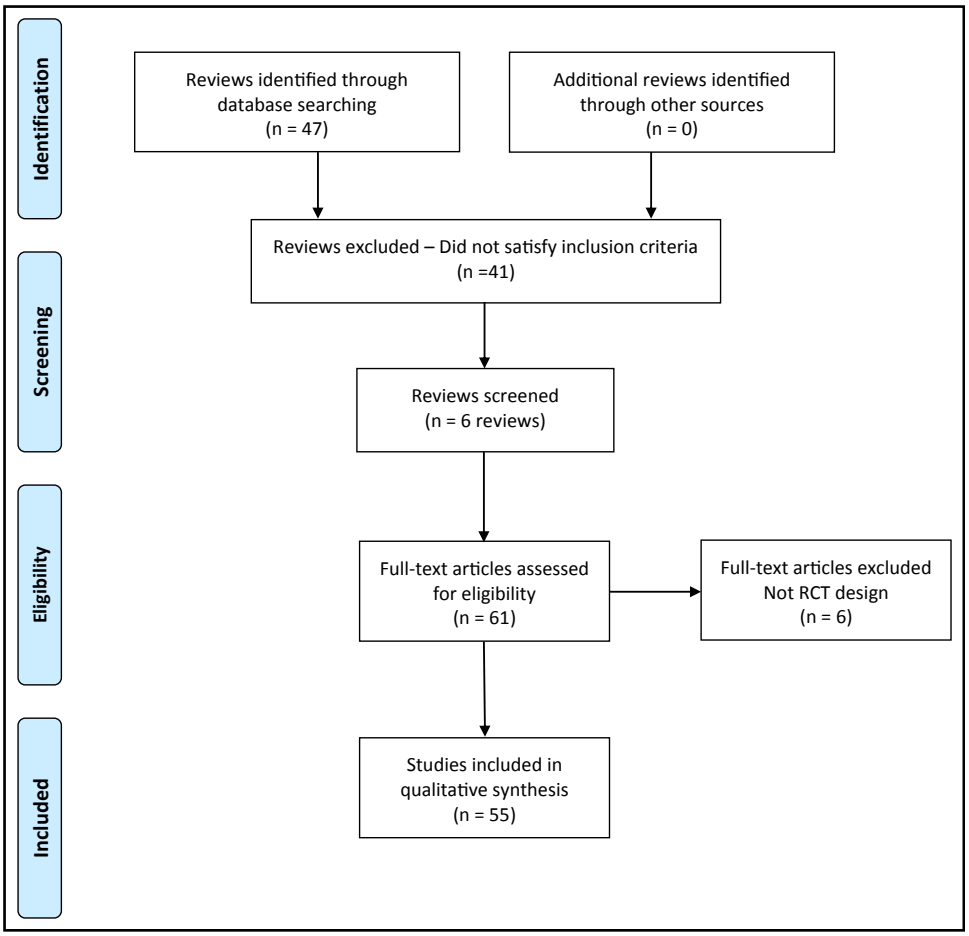

Fig. PRISMA diagram of article retrieval.

(K.O.) participated. Final decisions were made when agreement among the 3 evaluators was achieved.

Data items and collection

We created and piloted a customized data collection form. The following data were then extracted from the studies: randomization, allocation concealment, number randomized, number analyzed, and missing data strategy. The data extraction was performed by 2 authors independently and in duplicate (K.B.S.L.B. and B.T.). Any disagreements were resolved by discussion with the third author (K.O.). We attempted to contact the authors for any missing information.

Risk of bias or quality assessment in individual studies

All studies that reported or did not report and conducted or did not conduct ITT analysis were assessed concerning the risk of attrition bias using the Cochrane Collaboration's risk of bias tool.

RESULTS

We identified 47 Cochrane systematic reviews in the initial search. From these, 17 were duplicates, 21 were excluded with reasons, and 9 satisfied the inclusion criteria. From the full review assessment, a further 3 reviews were excluded, because 2 were not RCTs, and 1 was an ongoing study (Supplementary material 1).

A total of 6 reviews were assessed, and 61 potential RCTs were identified from these reviews. These RCTs were produced from 1984 to 2016. From the full article assessment, a further 6 studies were excluded because they were not RCTs. As a result, our final sample comprised 55 RCTs (Supplementary material 2), including 3 split-mouth trials (Fig). Overall, the agreement was high between the 2 evaluators (83.6%). Thus, the third evaluator participated for only 9 studies (16.4%).

The results from the sample analyzed are shown in Table 1. From the 55 RCTs, 6 reported using an ITT approach. From these, only 1 study had a true ITT

Table I. The sample analyzed and reported vs actual ITT practices

		Sample analyzed					
		Primary analysis, ITT	Sensitivity analysis, PP				
Reported using ITT	Conducted true ITT*	Full random sample	Sufficient dose	Completer sample	False inclusion	Unclear	Total number of approaches used
No (K = 49)	12 (24%)	12 (18%)	10 (15%)	19 (28%)	5 (7%)	21 (31%)	67†
Yes (K = 6)	1 (17%)	1 (8%)	1 (8%)	4 (33%)	2 (17%)	4 (33%)	12
Total (K = 55)	13 (24%)	13 (16%)	11 (14%)	23 (29%)	7 (9%)	25 (32%)	79

Column descriptions: (1) full random sample (analyses involved the total randomized numbers), (2) sufficient dose (analyses conducted on only participants who received a minimum amount of medication/treatment), (3) completer sample (analyses conducted on only patients who completed the medication or treatment phase), (4) false inclusion (after randomization, the participant did not meet the inclusion criteria and was removed from the analyses), and (5) unclear (insufficient information to determine the sample analyzed).
K, study.
*Only category (1), full random sample, was considered a true ITT strategy.
†The values in each row of Table I do not sum to the total number of studies in the first column (ie, "reported using ITT") because some studies used multiple analyses in the same study.

Table II. Missing data strategies for ITT and other analytic practices

	Missing data strategy						
		Imputation*		Sensitivity analysis			
Conducted true ITT	No dropout	Multiple imputation	Missing = failure	All followed up	Sample followed up	Unclear	Total number of approaches used
No (K = 31)	0 (0%)	1 (3%)	1 (3%)	0 (0%)	30 (81%)	5 (14%)	37†
Yes (K = 13)	11 (79%)	0 (0%)	1 (7%)	1 (7%)	0 (0%)	1 (7%)	14
Unknown (K = 11)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	11 (100%)	11
Total (K = 55)	11 (18%)	1 (2%)	2 (2%)	1 (2%)	30 (48%)	17 (28%)	62

Column descriptions: (1) no dropout, (2) imputation and its variations: multiple imputation (replacement of each missing value with a plausible value analyzed by using standard procedures for complete data and combining the results from these analyses), and missing = failure (classified missing data as treatment failure), (3) all followed up (all participants, including dropouts, were followed), (4) sample followed up (analyses of participants whom the researchers could follow), and (5) unclear (no information provided or unclear).
K, Study.
*Only the variations of imputation observed were included.
†The values in each row of Table II do not sum to the total number of studies in the first column (ie, "conducted true ITT") because some studies used multiple strategies in the same study.

analysis (2%). From the 49 RCTs that did not report using an ITT analysis, 12 had in fact carried out an ITT analysis (22%). When we looked at the sample analysis, we found that the most frequently used method was the "completer sample," with 19 studies (28%). "Full random sample" and "sufficient dose" were similar, with 13 and 11 studies adopting this method, respectively (16% and 14%). "False inclusion" came next with 7 studies (9%). It was not possible to determine the sample analyzed in 25 studies (32%), which were considered "unclear."

Most of the studies were PP analyses. The categories representing PP analysis ("completer sample," "sufficient dose," and "false inclusion") corresponded to 52% of the studies. The category representing ITT analyses ("full random sample") corresponded to 16% of the studies.

The results from the missing data strategy are shown in Table II. We have included in this table the only analyses which were used by any study. For studies that did not conduct a true ITT analysis, the most-used missing data strategy was "sample followed up," with 30 studies (81%). The categories "multiple imputation" and "missing = failure" came next, with 1 study each (3%). It was not possible to determine the missing data strategy in 5 studies (14%) that were considered "unclear."

For the studies that conducted a true ITT analysis, the most observed missing data strategy was "no dropout,"

Table III. Trials that reported ITT and conducted or not true ITT, with quotations verbatim, reasons, and risk of attrition bias

Trial	*Reported ITT*	*Conducted true ITT*	*Quotation verbatim*	*Reasons*	*Risk of attrition bias*
Banks 2004	Yes	No	"…we recruited over 200 patients with an intention to treat analysis."	The authors randomized 203 patients and analyzed 136, according to Figure 3	High
Cirgic 2016	Yes	No	"In the analysis, the total sample was considered as an ITT group, which comprised all subjects, here called ITT group."	The authors randomized 105 patients and analyzed 97, according to Figure 2	Unclear
Ghafari 1998	Yes	No	"Of the original 84 children recruited to the study, 21 (25%) were discontinued for lack of cooperation, a term we differentiate from compliance (Table I) …. Eventually, all patients will be included in an intent-to-treat analysis."	The authors only analyzed 63 patients from the 84 recruited, according to Table II	High
Lee 2007	Yes	No	"Six patients failed to complete the 12-month protocol. No patients were excluded from the trial on the grounds of poor treatment response, and when poor compliance was suspected, the trial protocol was adhered to and final radiographs were taken on an intention-to-treat basis."	The authors excluded the 6 patients who failed in the final analysis according to Figure 5 and Table I	Low
North Carolina 2004	Yes	No	"As is frequently done in clinical trials, 2 groups of patients were defined for analysis, an "intent to treat" (ITT) sample, which comprised all patients (n = 166) who had completed phase 1."	The authors analyzed only 137 patients, according to Table II	Unclear
Pétren 2008	Yes	Yes	"Data on all patients were analyzed on an intention-to-treat (ITT) basis."	All patients were analyzed, according to Figure 5	Low

with 11 studies (79%). The categories "all followed up," "missing = failure," and "unclear" came next, with 1 study each (7%). The criteria used to distinguish between trials that reported an ITT analysis and those that did not, as well as those that conducted a true ITT analysis and those that did not, are presented in Tables III and IV.

Considering the total number of studies, the strategy "sample followed up" was the most used (30 studies, 48%). The second was "no dropout" (11 studies, 18%). "Missing = failure" was the third, with 2 studies (2%). "All followed up" and "multiple imputation" came next, with 1 study each (2%). It was not possible to determine the missing data strategy in 17 studies (28%) that were considered "unclear."

Regarding the risk of attrition bias, from the 5 studies that reported ITT and did not conduct it, 2 had a high risk of attrition bias, 2 were unclear, and 1 was considered at low risk. One study that reported and conducted ITT was considered at low risk of attrition bias (Table III). From the 12 studies that conducted a true ITT analysis, 8 were considered at low risk of attrition bias, 2 were considered unclear, and 2 were not assessed (Table IV).

DISCUSSION

Our findings provide valuable information about the use of ITT and missing data strategy in orthodontic trials.

In this respect, it is concerning that only 2% of the studies reported using ITT analysis. From the 49 studies that did not report using ITT, 11 did not have dropouts and were therefore classified as using ITT from this review. Forty-one of the 55 studies did not report or use ITT analysis.

Table IV. Trials that did not report, but conducted true ITT, with quotations verbatim, reasons, and risk of attrition bias

Trial	*Reported ITT*	*Conducted true ITT*	*Quotation verbatim*	*Reasons*	*Risk of attrition bias*
Alikhani 2013	No	Yes	"Twenty patients were recruited and completed the study with no loss to follow-up."	There were no dropouts	Low
Arun 1994	No	Yes	"Following the completion of the tracing and measurements of the 120 cephalograms obtained from the 60 subjects at the beginning and end of the treatment…"	There were no dropouts	Low
Atalay 2010	No	Yes	No quotation	There were no dropouts, according to Table III	Low
Bondemark 2005	No	Yes	"Thus, 40 patients were randomized, 20 (10 girls and 10 boys) were allocated to receive treatment with the IOA, and 20 (12 girls and eight boys) with the EOA. All 40 patients completed the trial."	There were no dropouts	Low
Erbay 1995	No	Yes	No quotation.	There were no dropouts, according to Tables II and III	Not assessed
Fischer 2007	No	Yes	"All patients were treated successfully to completion."	There were no dropouts	Low
Godoy 2011	No	Yes	"All children treated in this trial with both appliances had their crossbite corrected."	There were no dropouts	Low
Keles 2002	No	Yes	No quotation.	There were no dropouts, according to Tables I and II	Unclear
Killiardis 1990	No	Yes	No quotation.	There were no dropouts, according to Table I.	Not assessed
Oliveira 2004	No	Yes	No quotation.	There were no dropouts, according to Tables I and II	Low
Ramoglu 2010	No	Yes	No quotation.	There were no dropouts, according to Table	Low
Thiruvenkatachari 2010	No	Yes	"Even though the trial was stopped early, we carried out the data analysis for all 64 patients who started treatment."	There were no dropouts	Unclear

Our results are similar to a previous study in which the authors also evaluated ITT analysis in orthodontic RCTs.[16] They found that 6% of the RCTs applied and reported the ITT analysis correctly, whereas most performed a PP analysis instead. However, their source was different from ours. Although we used RCTs from the Cochrane database, they evaluated RCTs from 5 journals.

It was reassuring that our results were similar to other studies in medicine. For example, in a survey of 119 RCTs in which the authors stated that they had done an ITT analysis, only 34 (29%) had conducted a true ITT analysis.[15] In our study, from the 6 RCTs that stated a true ITT analysis, only 1 (17%) actually conducted a true ITT analysis.

Another study in pharmacotherapy evaluated the ITT analyses and missing data approaches for alcohol use disorders and reported that only 37% had done a true ITT analysis.[11] Similarly, in our survey, 22% of the studies conducted a true ITT analysis.

Our results showed that the recommendation of using ITT analysis is not followed in the reporting of orthodontic trials. Currently, the PP analysis is the most frequently used analysis. This misusing may be due to a lack of understanding about ITT analysis, PP analysis, and missing data strategy. This lack of understanding was confirmed in a study that systematically investigated how authors defined ITT with missing outcome data. There is no consensus on the definition of ITT for missing outcome data.[18]

This lack of understanding has several consequences. First, if an ITT analysis is carried out, the inclusion of values for dropouts may lead to more conservative results with potential reductions of false-positive findings (type I error) and possible increases of false-negative findings (type II error). Conversely, if PP analysis is carried out, the exclusion of information from omitted subjects can overestimate the effect of the treatment, increasing the possibility of false-positive findings and decreasing the likelihood of false-negative findings.[15,19] Another chance for overestimation or underestimation of the effects of treatment can occur if patients completing the trial tend to favor more or less the experimental arm than the excluded patients. The possibility of false-negative results can also be related to a small sample size.

This duality gives rise to consider whether investigators should conduct both forms of analysis. This conduction is recommended to establish equivalence or noninferiority in trials.[20] It also seems reasonable to perform both analyses in superiority trials, where the internal validity of the outcomes will be highlighted if the PP analysis supports the ITT analysis.[21]

If these steps are taken, this will enable clinicians to provide information to their patients that reflects their levels of cooperation. For example, when we consider the ITT analysis, this lets us inform our patients of the average effect of treatment for an average patient. That is, the results include the effects when patients do not comply with treatment protocols, reflecting the "real world" of the care. However, if we use the PP data, we could inform our patients of the effect of treatment in an ideal setting.

Missing data strategy

Considering the total number of studies, the strategy "sample followed up" was the most observed in our survey (48% of the studies). This outcome is different from a study in medicine, where last observation carried forward and sensitivity analyses appeared to be the most observed (50% of the studies each), followed by imputation of missing data, used in 46% of the studies.[18] In this review, "last observation carried forward" was not observed in any of the studies, and "multiple imputation" was observed in only 1 study. However, our results for sensitivity analysis for missing data strategy (Table II) were similar (50%). These outcomes highlight some differences regarding how authors deal with missing outcome data in dentistry and medicine. This information is relevant for future studies in dentistry when the multiple imputation of values and sensitivity analysis have been recommended as the missing data strategy in RCTs.[22-24]

In our study, the method used for managing missing data was "unclear" in 28% of the studies. This result was similar to the outcome of a systematic review that assessed the reporting, extent, and handling of loss to follow up. It was found that the method by which loss to follow up was handled was unclear in 19% of the studies.[3]

Finally, the most used missing-data strategy for authors who conducted a true ITT analysis was "no dropout." These results highlight the importance of preventing dropouts and missing data in studies, since this is a guarantee of conducting a true ITT analysis. Nevertheless, this is quite difficult and not always achievable because of the duration of orthodontic treatment.

Risk of attrition bias

Regarding the risk of attrition bias, overall, when we looked at the studies, there was poor evaluation of attrition bias from the systematic reviewers. For example, from the 5 studies that reported ITT and did not conduct it, 2 were considered at unclear risk of attrition bias, and 1 was considered at low risk of attrition bias (Table III). However, these 3 studies were clearly at high risk of bias. When we looked at the 13 studies that conducted a true ITT analysis (1 study reported and conducted and 12 did not report and conduct), there was a better evaluation of attrition bias from the systematic reviewers. For example, of the 13 studies, 9 were considered at low risk of attrition bias, 2 were considered unclear, and 2 were not assessed (Tables III and IV). Nevertheless, the 13 studies were at low risk of attrition bias. These results agree with those from a systematic survey on the reporting and handling of missing outcome data in Cochrane systematic reviews in mental health; it also indicated poor evaluation.[25]

Limitations

We decided to restrict our data to trials included in Cochrane reviews because this added a level of quality control. It was also relevant because we wished to illustrate this question from high-quality systematic reviews. As a result, we did not include other sources.

Suggestions

Finally, we believe that we can make some recommendations from our findings. We suggest that investigators should (1) develop a plan to manage dropouts and missing data before the trial; (2) use ITT analysis to deal with dropouts; (3) perform PP analysis to support ITT analysis; (4) describe how dropouts and missing data were managed; and (5) give the reasons for the dropouts and the missing data.

CONCLUSIONS

There is a lack of understanding of ITT and missing data strategy in orthodontic research. As a result, the overall picture of the use of ITT analysis in orthodontics may result in the uncertain interpretations of data, leading to overestimation of treatment effects. The use of ITT analysis should be considered in all orthodontic trials.

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APPENDIX

Supplemental material 1. Included and excluded reviews from search in Cochrane library

Included	*Title*	*Cause*
No	Adhesives for fixed orthodontic bands	No treatment
No	Adhesives for fixed orthodontic brackets	No treatment
No	Adhesives for fixed orthodontic brackets	Translation
No	Casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) for the prevention of white spots on teeth in patients wearing fixed orthodontics braces	No treatment
No	Direct versus indirect bonding for bracket placement in orthodontic patients	No treatment
No	Enamel etching for bonding fixed orthodontic braces	No treatment
No	Enamel etching for bonding fixed orthodontic braces	Translation
No	Initial arch wires for tooth alignment during orthodontic treatment with fixed appliances	Arch wires
No	Initial arch wires for tooth alignment during orthodontic treatment with fixed appliances	Translation
No	Initial arch wires for tooth alignment during orthodontic treatment with fixed appliances	Translation
No	Interdental cleaning in patients with fixed orthodontic appliances	No treatment
No	Interspace/interdental brushes for oral hygiene in orthodontic patients with fixed appliances	No treatment
No	Interspace/interdental brushes for oral hygiene in orthodontic patients with fixed appliances	Translation
No	Interventions for managing relapse of the lower front teeth after orthodontic treatment	Translation
No	Interventions for managing relapse of the lower front teeth after orthodontic treatment	No RCTs
No	Interventions for space closure in orthodontic treatment	Withdraw
No	Interventions for the management of gingivitis in fixed orthodontic patients	No treatment
No	Laceback ligatures for controlling anchorage in patients undergoing fixed orthodontic treatment	No treatment
No	Non-pharmacological interventions for alleviating pain during orthodontic treatment	No treatment
No	Non-surgical adjunctive interventions for accelerating tooth movement in patients undergoing fixed orthodontic treatment	Translation
No	Non-surgical adjunctive interventions for accelerating tooth movement in patients undergoing fixed orthodontic treatment	No treatment
No	Optimum force for tooth movement in orthodontic treatment	No treatment
No	Orthodontic and orthopaedic treatment for anterior open bite in children	Translation
Yes	Orthodontic and orthopaedic treatment for anterior open bite in children	Included
No	Orthodontic treatment for bimaxillary proclination in children and adults	Protocol
No	Orthodontic treatment for crowded teeth in children	Ongoing
No	Orthodontic treatment for deep bite and retroclined upper front teeth in children	No RCTs
No	Orthodontic treatment for deep bite and retroclined upper front teeth in children	Translation
Yes	Orthodontic treatment for distalising upper first molars in children and adolescents	Included
No	Orthodontic treatment for distalising upper first molars in children and adolescents	Translation
Yes	Orthodontic treatment for posterior crossbites	Included
No	Orthodontic treatment for posterior crossbites	Translation
No	Orthodontic Treatment for Posterior Crossbites	Translation
Yes	Orthodontic treatment for prominent lower front teeth (Class III malocclusion) in children	Included
No	Orthodontic treatment for prominent lower front teeth (Class III malocclusion) in children	Translation
Yes	Orthodontic treatment for prominent upper front teeth (Class II malocclusion) in children	Included
No	Orthodontic treatment for prominent upper front teeth (Class II malocclusion) in children	Translation
No	Orthodontics for treating temporomandibular joint (TMJ) disorders	Withdraw
No	Orthodontics for treating temporomandibular joint (TMJ) disorders	Translation
No	Pharmacological interventions for pain relief during orthodontic treatment	No treatment
No	Reinforcement of anchorage during orthodontic brace treatment with implants or other surgical methods	No treatment
No	Reinforcement of anchorage during orthodontic brace treatment with implants or other surgical methods	Translation
No	Retention procedures for stabilising tooth position after treatment with orthodontic braces	No treatment
No	Retention procedures for stabilising tooth position after treatment with orthodontic braces	Translation
No	Self-ligating orthodontic braces for straightening teeth	Protocol
No	Surgical adjunctive procedures for accelerating orthodontic treatment	Surgery
No	Surgical adjunctive procedures for accelerating orthodontic treatment	Translation

Supplemental material 2. Studies included in the review with Pub Med Identifiers (PMID)

Study	*Title*	*PMID*
Aboul-Ela 2011	Mini screw implant-supported maxillary canine retraction with and without corticotomy-facilitated orthodontics	21300255
Acar 2010	Molar distalization with a pendulum appliance K-loop combination	20231213
Alali 2014	A prospective controlled evaluation of Class II division 1 malocclusions treated with fixed lingual mandibular growth modificator	23987240
Alikhani 2013	Effect of micro-osteo perforations on the rate of tooth movement	24182579
Altug-Atac 2008	Three-dimensional bimetric maxillary distalization arches compared with a modified Begg intraoral distalization system	17947349
Armi 2011	Effect of RME and headgear treatment on the eruption of palatally displaced canines: A randomized clinical study	21299387
Arun 1994	A cephalometric comparison of mandibular headgear and chip-cap appliances in orthodontic and orthopaedic view points	9582620
Atalay 2010	Dentofacial effects of a modified tandem traction bow appliance	20348164
Baccetti 2008	A randomized clinical study of two interceptive approaches to palatally displaced canines	18524761
Banks 2004	Incremental versus maximum bite advancement during Twin-block therapy: A randomized controlled clinical trial	15520691
Baysal 2014	Soft tissue effects of Twin Block and Herbst appliances in patients with Class II division 1 mandibular retrognathy	21357655
Bilgic 2011	Comparison of the effects of fixed and removable functional appliances on the skeletal and dentoalveolar structures	22372266
Bondemark 2005	Extraoral vs Intraoral Appliance for Distal Movement of Maxillary First Molars: A Randomized Controlled Trial	16279817
Burhan 2014	Dentoskeletal effects of the Bite-Jumping Appliance and the Twin-Block Appliance in the treatment of skeletal Class II malocclusion: a randomized controlled trial	25296729
Cevidanes 2003	Clinical outcomes of Fränkel appliance therapy assessed with a counterpart analysis	12695764
Cirgic 2016	Treatment of large overjet in Angle Class II: division 1 malocclusion with Andresen activators versus prefabricated functional appliances—a multicenter, randomized, controlled trial	26543061
Cura 1997	The effect of treatment with the Bass appliance on skeletal Class II malocclusions: A cephalometric investigation	9458602
Elkordy 2016	Three-dimensional effects of the mini-implant–anchored Forsus Fatigue Resistant Device: A randomized controlled trial	25989213
Erbay 1995	The effects of Frankel's function regulator (FR-4) therapy on the treatment of Angle Class I skeletal anterior open bite malocclusion	7598110
Ferreira 2006	A prospective study of the treatment effects of a removable appliance with palatal crib combined with high-pull chincup therapy in anterior open-bite patients	16527639
Fischer 2007	Orthodontic Treatment Acceleration with Corticotomy-assisted Exposure of Palatally Impacted Canines	17465647
Florida 1998	Anteroposterior skeletal and dental changes after early Class II treatment with bionators and headgear	9457018
Garib 2005	Rapid Maxillary Expansion—Tooth Tissue-Borne Versus Tooth-Borne Expanders: A Computed Tomography Evaluation of Dentoskeletal Effects	16097223
Ghafari 1998	Headgear versus function regulator in the early treatment of Class II, Division 1 malocclusion: A randomized clinical trial	9457019
Godoy 2011	Treatment of posterior crossbite comparing 2 appliances: A community-based trial	21195256
Karacay 2006	Forsus Nitinol Flat Spring and Jasper Jumper Corrections of Class II division 1 Malocclusions	16808575
Keles 2002	Effect of Varying the Force Direction on Maxillary Orthopedic Protraction	12401046
Kiliaridis 1990	Anterior open bite treatment with magnets	2086265
Kilic 2008	A comparison of dentoalveolar inclination treated by two palatal expanders	18276928
Lagravere 2010	Transverse, vertical, and anteroposterior changes from bone-anchored maxillary expansion vs traditional rapid maxillary expansion: A randomized clinical trial	20197161
Lamparski 2003	Comparison of skeletal and dental changes between 2-point and 4-point rapid palatal expanders	12637904
Lee 2007	A controlled clinical trial of the effects of the Twin Block and Dynamax appliances on the hard and soft tissues	17456506
Lee 2014	An extended period of functional appliance therapy: a controlled clinical trial comparing the Twin Block and Dynamax appliances	23291502
Leethanakul 2014	Interseptal bone reduction on the rate of maxillary canine retraction	24592904
Lipolld 2013	Early treatment of posterior crossbite – a randomised clinical trial	23339736

Supplemental material 2. Continued

Study	*Title*	*PMID*
London 1998	A prospective evaluation of Bass, Bionator and Twin Block appliances. Part 1 – the hard tissues	9825553
Mandall 2010	Is early class III protraction facemask treatment effective? A multicentre, randomized, controlled trial: 15-month follow-up	20805344
Mao 1997	The Correction of Class II, Division 1 Malocclusion with Bionator Headgear Combination Appliance	9812793
Martina 2012	Transverse changes determined by rapid and slow maxillary expansion – a low-dose CT-based randomized controlled trial	22812438
Martina 2013	Efficacy of the Sander bite-jumping appliance in growing patients with mandibular retrusion: a randomized controlled trial	23323608
McNally 2005	A randomized controlled trial comparing the quadhelix and the expansion arch for the correction of crossbite	15784941
New Zealand 1996	Maxillary and cranial base changes during treatment with functional appliances	8659471
North Carolina 2004	Outcomes in a 2-phase randomized clinical trial of early Class II treatment	15179390
Oliveira 2004	Three-dimensional assessment of morphologic changes of the maxilla: A comparison of 2 kinds of palatal expanders	15356500
Papadopoulos 2010	Noncompliance maxillary molar distalization with the First Class Appliance: A randomized controlled trial	20451774
Paul 2002	Upper removable appliance or Jones Jig for distalizing first molars? A randomized clinical trial	12416538
Petren 2008	Correction of unilateral posterior crossbite in the mixed dentition: A randomized controlled trial	18538237
Ramoglu 2010	Maxillary expansion in the mixed dentition: rapid or semi-rapid?	19797410
Showkatbakhsh 2011	Treatment effects of R-appliance and Anterior Inclined Bite Plate in Class II, Division 1 malocclusion	22230999
Thilander 1984	The effect of early interceptive treatment in children with posterior cross-bite	6583062
Thiruvenkatachari 2010	Comparison of Twin-block and Dynamax appliances for the treatment of Class II malocclusion in adolescents: A randomized controlled trial	20691354
UK (11-14) 2003	Effectiveness of treatment for Class II malocclusion with the Herbst or Twin-block appliances: A randomized, controlled trial	12923506
Vaughn 2005	The effects of maxillary protraction therapy with or without rapid palatal expansion: A prospective, randomized clinical trial	16168327
Xu 2001	The orthopaedic treatment of skeletal class III malocclusion with maxillary protraction therapy	———————
Yaqoob 2012	Use of the Clark Twin Block functional appliance with and without an upper labial bow: a randomized controlled trial	21848509