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Personalizing orthodontics – precision health methods in orthodontic clinical trials

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Personalizing orthodontics – precision health methods in orthodontic clinical trials

Elizabeth J. Eve, D.M.D.

Abstract

Precision medicine optimizes treatment for the individual rather than the average patient typically described in clinical trials. Unique factors such as genetics, anatomy, and past environmental exposures influence how each patient responds to treatment. This phenomenon is known as heterogeneity of treatment effects or HTE. It is not known how often HTE is assessed in the orthodontic literature. The aim of this study was to investigate HTE reporting and the characteristics of recent trials that have analyzed HTE in major orthodontic specialty journals.

Randomized clinical trials (RCTs) published in European Journal of Orthodontics, American Journal of Orthodontics and Dentofacial Orthopedics, Angle Orthodontist, Korean Journal of Orthodontics, and Orthodontics and Craniofacial Research from 2012 – 2016 were identified and searched for HTE results. Characteristics of these RCTs were described.

Of the 175 RCTs identified, 20 (11.43%) met the HTE inclusion criteria. Studies with and without HTE reporting were similar in many aspects, such as number of subjects enrolled, but differed in study design and number of hypothesis tests performed with fewer tests in RCTs reporting HTE (median: 10.5 tests) than not (median: 24 tests).

HTE keyword terminology could be valuable to incorporate as momentum builds surrounding precision health and personalized treatment. When terms such as ‘subgroup’ or ‘interaction’ are used, readers and reviewers are alerted that differences in treatment response among patient subgroups have been assessed. Investigators have the opportunity to increase the impact of their work by evaluating whether certain patient characteristics cause HTE.

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Introduction

Precision medicine optimizes treatment for the individual rather than the average patient typically described in clinical trials. Unique factors such as genetics, anatomy, and past environmental exposures influence how each patient responds to treatment. This phenomenon is known as heterogeneity of treatment effects or HTE. The National Institutes of Health requires that Phase III clinical trials analyze if and how characteristics such as age or gender cause subgroups of people to respond differently to a healthcare intervention.[1] Knowledge about qualities that make certain patients better candidates for one treatment over another has the potential to make healthcare more effective and economical.[2]

The precision medicine approach is relevant in dentistry and orthodontics.[3-6] For example, it has been demonstrated that genetic variants cause certain patients to be more susceptible to external apical root resorption during orthodontic treatment.[4] This data informs treatment options and, in the future, might indicate prescription of targeted medicines that reduce the risk for root resorption during orthodontics.[5] As basic science continues to elucidate the pathways underlying jaw development and tooth movement, orthodontists will have the opportunity to incorporate their patients' genetic profiles into treatment planning and appliance design.[5,6]

In current orthodontic practice, however, it is not practical to perform expensive genetic tests as part of the diagnostic workup. Even without these resources, orthodontists routinely apply the principles of precision health to deliver customized treatment for different malocclusions. For example, Bjork identified anatomic characteristics that predict skeletal growth patterns[7] and this information influences the treatment approach in growing patients. It is

possible that additional patient characteristics customarily recorded during the clinical exam and diagnostic records predict how an individual will respond to treatment.

As orthodontists strive to improve clinical outcomes and decrease treatment time by customizing care for their patients, it is increasingly valuable to have a strong evidence base to inform decisions regarding heterogeneity of orthodontic treatment effects. To our knowledge, HTE practices have not been examined in the orthodontic literature. Our aim is to investigate HTE reporting and the characteristics of the trials that have analyzed HTE in major orthodontic specialty journals over the past five years.

Material and Methods

The reporting of heterogeneity of treatment effects (HTE) was assessed in randomized clinical trials (RCTs) published in the five orthodontic specialty journals with the highest impact factor (IF) in 2016 *(2016 Journal Citation Reports® (Clarivate Analytics, 2017))*:[8]

1. European Journal of Orthodontics (IF: 1.62)
2. American Journal of Orthodontics and Dentofacial Orthopedics (IF: 1.47)
3. Angle Orthodontist (IF: 1.37)
4. Korean Journal of Orthodontics (IF: 1.18)
5. Orthodontics and Craniofacial Research (IF: 1.12)

For the purposes of this study, RCT was defined as a prospective comparison of two or more randomly assigned interventions performed in human subjects. Studies in which data collection was *ex vivo*, such as on extracted premolars, were considered to be human studies if the intervention was done while the teeth were in the subject's mouth.

Electronic databases of the five aforementioned journals were searched for RCTs published from 1/1/2012 to 12/31/2016. Randomized trials were identified by searching the full article text for the term "random", which encompasses all iterations of the word, e.g., randomized and randomly.[9] Articles containing "random" were handsearched and included if the term was used to describe allocation of treatment to study participants. Studies that reported non-original data, i.e., published elsewhere or secondary outcomes from a previously published study, were excluded, as were pilot and safety studies. Articles were identified by EE, SB, and JB and discrepancies were resolved by discussion with AL.

The following characteristics were recorded for each eligible RCT: journal of publication,[9-12] journal impact score at time of publication,[11,13] country of publication,[9,10,14] study

design (parallel, crossover or split mouth),[10,13] whether the title contained "randomized controlled trial" or "randomized clinical trial," number of individual human subjects randomized,[9,10,13-16] whether a statistical test was done to compare baseline characteristics between study groups,[14,17] whether an intention-to-treat analysis was reported, total number of unique hypothesis tests identified in figures and tables, whether there was adjustment for multiple comparisons,[11,16] whether the primary endpoint was statistically significant,[12,13,15] and presence of keywords (subgroup, heterogeneity, interaction, modifier, stratified or strata) suggesting analysis of HTE.

Articles that were published online and in print on different dates were assigned to the year of print publication. Studies published only electronically in 2016 and not scheduled to appear in print until 2017 were excluded. The country of publication was designated as the country where ethical approval for the study was obtained. Whether the primary endpoint was statistically significant could not be reported because the primary outcome variable was ambiguous.

Guidelines for conducting analysis of heterogeneity of treatment effects or subgroup analysis are included in the Consolidated Standards of Reporting Trials (CONSORT) statement,[18] which provides a framework for reporting randomized clinical trials and has been adopted by over 400 journals,[19] including AJODO,[20] EJO,[21] and OCR.[22] Subgroup analysis often consists of a statistical test for interaction.[23-25] Other HTE approaches include subpopulation treatment effect pattern plots (STEPP),[26,27] the Johnson-Neyman type approach,[28,29] and fractional polynomial models.[30] When subgroup analysis is used to identify heterogeneity of treatment effects, the interaction should be between a patient characteristic and clinical intervention.

As our primary interest is to describe the reporting of patient differences in response to randomized treatments, any studies with terms 'subgroup,' 'heterogeneity,' 'interaction,' 'modifier,' 'stratified,' or 'strata' used in a context other than to describe HTE did not meet the keyword inclusion criteria. For example, RCTs with HTE keywords pertaining to the variability in treatment effects over time, the randomization strategy, or an unrelated topic, such as the term "interaction" to demonstrate how a molecule contacts a receptor, were not included. Similarly, HTE keywords listed only in a preformatted section header and not repeated in the text did not meet the keyword criteria. This is relevant for RCTs that follow the CONSORT statement, which contains a line item for HTE (referred to as "subgroup analysis") on its checklist.[19]

Identification of HTE keywords and collection of the aforementioned study characteristics was performed by EE and SB with discrepancies resolved by discussion with AL. Inter-rater reliability was determined using Cohen's kappa coefficient to assess agreement between EE and SB regarding the HTE keyword search. Descriptive statistics were used to summarize HTE reporting (for continuous variables, medians and range; for categorical variables, frequencies and percentages). Data analysis was performed using Stata Statistical Software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Results

Of the 2,282 articles searched electronically, 175 (7.67%) randomized clinical trials were identified. Figure 1 shows the distribution of these studies by journal over time. The greatest number of RCTs was found in AJODO (65/175, 37.14%), which is published monthly; AO, EJO, and KJO are published bimonthly and OCR is published quarterly. In 2016, there was an increase in the overall number of RCTs with twice as many published in AO compared to previous year.

Forty-eight (27.43%) articles included keywords suggestive of analysis of heterogeneity of treatment effects. There was substantial agreement between investigators regarding HTE keyword identification (94.28%, kappa = 0.78). Twenty-eight (58.33%) of the RCTs with HTE keywords did not meet HTE eligibility for one or two of the following reasons: keywords described an interaction with time (13), were located only in a preformatted section header (12), pertained to randomization or another aspect of the study that was not clearly HTE (7), or were used in a different context, such as another definition of the word or to explain future research objectives (6). A total of twenty studies (11.43%) contained HTE keywords consistent with the inclusion criteria (Figure 2).

Table I summarizes the study characteristics observed overall and for trials with and without HTE keywords. The median impact score of all journals over the 5-year time period was 1.44 (range: 0.37 to 1.69). Over the five-year time period from 2012-2016, the greatest number of RCTs with HTE results was reported in AJODO (45.00%). RCTs in OCR and EJO were most likely to report HTE at 20.00% and 18.75%, respectively. Sixty percent of the RCTs with HTE were published in 2013 and 2014 with only 5.00% published in 2012, 15.00% published in 2015, and 20.00% published in 2016. HTE reporting was higher in studies originating from North

America (20.00%), South America (16.67%), and Europe (14.29%) compared to Asia (7.25%) and other continents (0.00%). Europe contributed the most studies with HTE results (40.00%).

RCTs with a parallel design were most common (67.43%) and had less HTE reporting (5.93%) compared to other study designs. Less than half (39.43%) of the trials that met our RCT inclusion criteria included the phrase “randomized clinical trial” or “randomized controlled trial” in the title. RCTs reporting statistical tests to compare baseline characteristics, intention-to-treat analysis, and adjustment for multiple comparisons were similar between articles with and without HTE results.

The median number of subjects randomized among all of the studies was 42 (range: 8 to 1,000). For studies with and without HTE, the median number of subjects randomized was 38 (range: 10 to 148) and 42 (range: 8 to 1,000) respectively. The median number of hypothesis tests presented in the tables and figures for all of the studies was 22 (range: 0 to 480). Studies reporting HTE had fewer hypothesis tests (median: 10.5; range: 0 to 217) than studies that did not report HTE (median: 24; range: 0 to 480).

Discussion

As personalized healthcare becomes routine and analysis of heterogeneity of treatment effects (HTE) is formally incorporated into clinical trials, orthodontists have the opportunity to make evidence based treatment decisions according to patients' individual characteristics. We observed that 11.43% (20/175) of randomized trials recently published in the highest impact orthodontic journals reported heterogeneity of treatment effects. The recent precision healthcare movement does not seem to have affected HTE reporting in the orthodontic literature, which decreased from 18.75% in 2014 to less than 10% in 2016.

We did not find that RCTs reporting HTE had a greater number of subjects than RCTs without HTE keywords (median: 38 and median: 42, respectively). This could be due to our observation that RCTs reporting HTE were more likely to have a split mouth or crossover design in which patients serve as their own controls. 65.00% of studies with HTE reporting had a split mouth or crossover design compared to only 28.39% of RCTs without HTE reporting. Studies that did not report HTE had a greater number of hypothesis tests than studies reporting HTE (median: 24 and median: 10.5, respectively). Because analysis of HTE requires additional hypothesis tests, we expected that RCTs with HTE results would report more hypothesis tests than RCTs without HTE results.

We found that HTE reporting in orthodontic RCTs (11.43%) was less than that reported in the medical literature (44-85%).[10,11,13-15,24] One possible explanation for this difference is our use of specific keywords to flag RCTs that might contain subgroup analysis. This approach was taken in an effort to maintain objectivity and identify the trials where analysis of HTE was made readily apparent. However, it is also a limitation because there are likely RCTs in our study that searched for patient differences in response to clinical treatments without using the terms

'subgroup,' 'heterogeneity,' 'interaction,' 'modifier,' 'stratified,' or 'strata.' Our results are consistent with a previous study by Pandis et al. that discussed ambiguity in the reporting of subgroup analysis in RCTs published in dental specialty journals.[8] Another limitation is that publications from only five select specialty journals were considered. Therefore, our results reflect only a portion of the RCTs that have recently contributed to the orthodontic field.

Orthodontic trials are somewhat restricted in their ability to analyze heterogeneity of treatment effects based on the number of subjects typically included. RCTs reporting subgroup analysis in the New England Journal of Medicine in 2007, for example, had a median number of 429 patients[15] compared to a median number of 42 patients in the studies identified in our assessment. Therefore, analysis of HTE in orthodontics might be best suited for meta-analysis that combine the results of multiple studies to increase the sample size.[31] Meta-analysis is especially valuable when it is conducted with raw data rather than the overall results from the contributing studies.[32] If individual responses to treatment are shared, then the data from orthodontic trials can be leveraged and we will have the opportunity to learn more about how patients with unique characteristics respond differently to orthodontic treatments. Future characterization of HTE in the orthodontic literature should include systematic reviews and meta-analyses.

Fueled by data from millions of cases, private industry is gaining an advantage in amassing the quantity of individual patient information[33] necessary to reveal heterogeneity of treatment effects. This will raise the bar for innovation in our specialty as patients come to expect faster and more personalized treatment. In order to stay competitive, it is integral that our specialty support communal efforts to conduct large-scale studies, such as the National Practice-Based Research Network, that have the power to analyze subgroup differences.[34] Retrospective

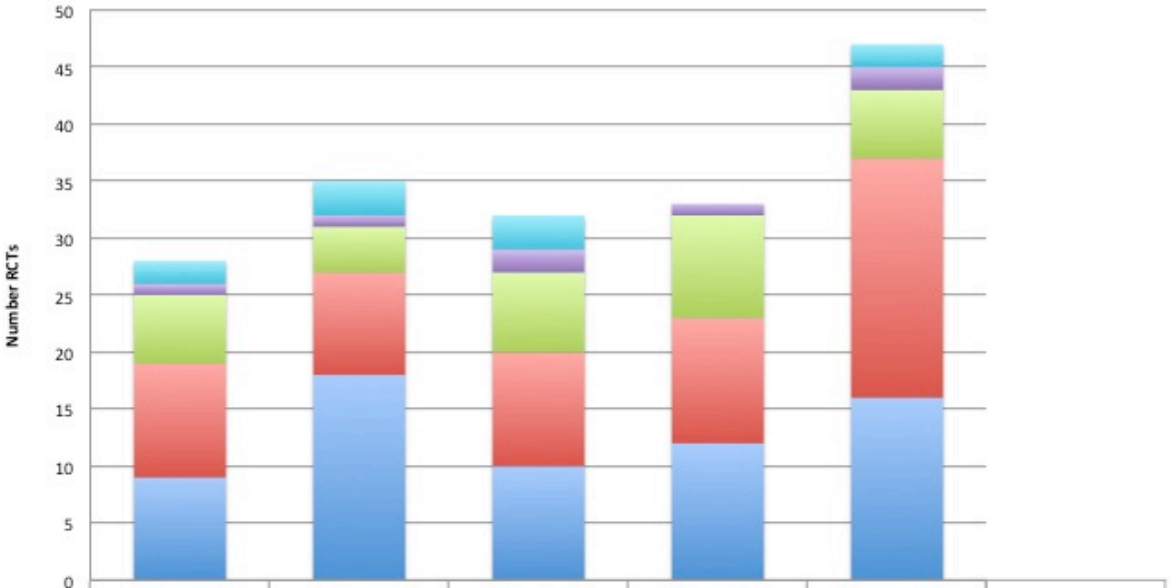
studies conducted with data from electronic medical records might also provide an enormous amount of information that could be used to determine how patients' unique medical histories or initial diagnoses influence their response to treatment.[2] Similarly, an "International Orthodontic Registry" as proposed by Ruf[35] could yield abundant information from a diverse pool of orthodontic patients so that HTE could be examined. We believe that as the field continues to progress, customized, highly efficient treatment will become pervasive, fueled by large data sets that facilitate studies on precision orthodontic care.

Conclusions

Our study showed that 11.43% of RCTs identified from major orthodontic specialty journals over the past five years reported HTE. The characteristics of the RCTs that did and did not report HTE varied. The HTE keyword terminology could be valuable to incorporate as momentum builds surrounding precision health and personalized treatment. When terms such as 'subgroup' or 'interaction' are used, readers and reviewers are alerted that differences in treatment response among patient subgroups have been considered. Investigators have the opportunity to increase the impact of their work by addressing patient characteristics that cause heterogeneity of treatment effects. Given the median sample size of 42 patients in orthodontic RCTs, HTE analysis might be more appropriate for larger studies, such as meta-analyses.

Figures

Figure 1. Number of randomized clinical trials (RCTs) published in each journal (%) from 2012 to 2016

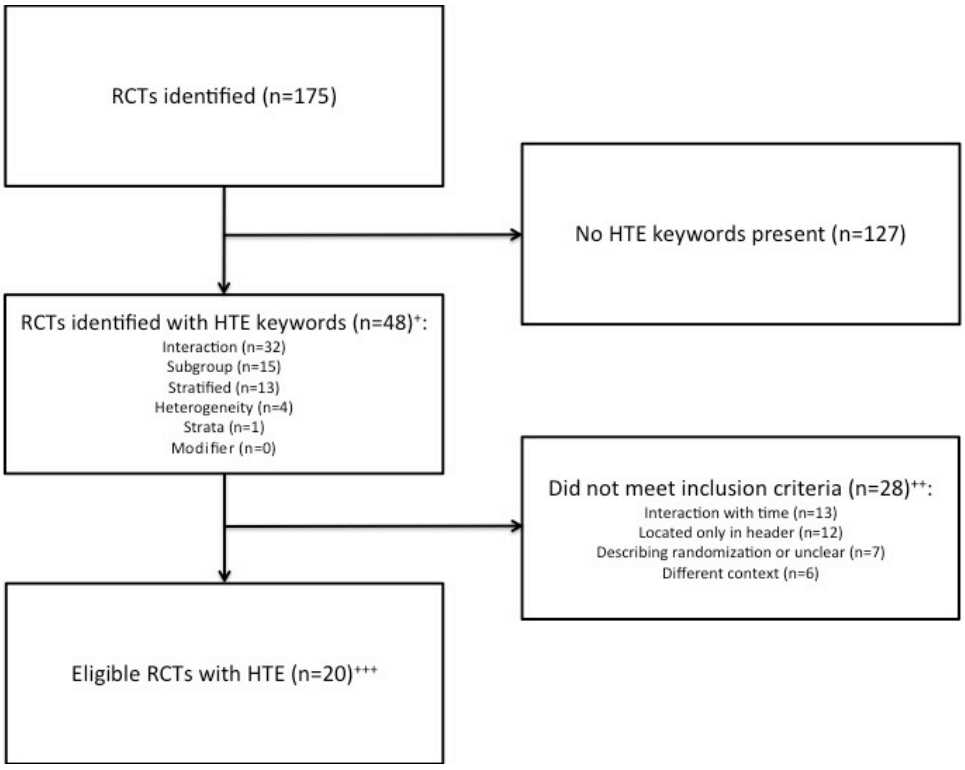


	2012	2013	2014	2015	2016	Total
OCR	2 (7.14)	3 (8.57)	3 (9.38)	0 (0.00)	2 (4.26)	10
KJO	1 (3.57)	1 (2.86)	2 (6.25)	1 (3.03)	2 (4.26)	7
EJO	6 (21.43)	4 (11.43)	7 (21.88)	9 (27.27)	6 (12.77)	32
AO	10 (35.71)	9 (25.71)	10 (31.25)	11 (33.33)	21 (44.68)	61
AJODO	9 (32.14)	18 (51.43)	10 (31.25)	12 (36.36)	16 (34.04)	65
Total	28	35	32	33	47	175

AJODO *American Journal of Orthodontics and Dentofacial Orthopedics*, AO *Angle Orthodontist*, EJO *European Journal of Orthodontics*, KJO *Korean Journal of Orthodontics*, OCR *Orthodontics and Craniofacial Research*

Column percentages might not add to exactly 100.00 due to rounding

Figure 2. Flowchart of heterogeneity of treatment effects (HTE) keyword identification



[+] 13/48 RCTs contained two HTE keywords. 2/48 RCTs contained three HTE keywords

[++] 10/28 RCTs with HTE keywords were excluded for two different reasons

[+++] 9/20 RCTs included contained at least one HTE keyword that was excluded, in addition to the keyword(s) that met the inclusion criteria

Reasons that RCTs with keywords did not meet inclusion criteria: 'interaction with time' if keyword describes patient differences over time; 'located only in header' if keyword is present in a preformatted section title, but not in text; 'describing randomization or unclear' if keyword describes randomization or another aspect of the study that is not clearly HTE; 'different context' if keyword is a homonym or explains future research objectives

Tables

Table I. Summary of randomized clinical trial (RCT) characteristics

Characteristic	RCT with HTE keywords (%) n = 20	RCT without HTE keywords (%) n = 155	Total (%) n = 175
Journal			
AJODO	9 (13.85)	56 (86.15)	65 (37.14)
AO	3 (4.92)	58 (95.08)	61 (34.86)
EJO	6 (18.75)	26 (81.25)	32 (18.29)
KJO	0 (0.00)	7 (100.00)	7 (4.00)
OCR	2 (20.00)	8 (80.00)	10 (5.71)
Year			
2012	1 (3.57)	27 (96.43)	28 (16.00)
2013	6 (17.14)	29 (82.86)	35 (20.00)
2014	6 (18.75)	26 (81.25)	32 (18.29)
2015	3 (9.09)	30 (90.91)	33 (18.86)
2016	4 (8.51)	43 (91.49)	47 (26.86)
Continent			
Asia	5 (7.25)	64 (92.75)	69 (39.43)
North America	4 (20.00)	16 (80.00)	20 (11.43)
South America	3 (16.67)	15 (83.33)	18 (10.29)
Europe	8 (14.29)	48 (85.71)	56 (32.00)
Other	0 (0.00)	12 (100.00)	12 (6.86)
Impact score			
Low	8 (9.09)	80 (90.91)	88 (50.29)
High	12 (13.97)	75 (86.21)	87 (49.71)
Study design			
Parallel	7 (5.93)	111 (94.07)	118 (67.43)
Split Mouth	9 (20.93)	34 (79.07)	43 (24.57)
Other	4 (28.57)	10 (71.43)	14 (8.00)
Entitled RCT			
Yes	8 (11.59)	61 (88.41)	69 (39.43)
No	12 (11.32)	94 (88.68)	106 (60.57)
Number of subjects randomized			
≤ 25	6 (13.64)	38 (86.36)	44 (25.14)
26 - 41	5 (11.90)	37 (88.10)	42 (24.00)
42 - 65	4 (8.89)	41 (91.11)	45 (25.71)
≥ 66	5 (11.36)	39 (88.64)	44 (25.14)
Baseline comparison test			
Yes	4 (8.89)	41 (91.11)	45 (25.71)
No	16 (12.31)	114 (87.69)	130 (74.29)
Intention-to-treat analysis			
Yes	2 (15.38)	11 (84.62)	13 (7.43)
No	18 (11.11)	144 (88.89)	162 (92.57)
Number of hypothesis tests			
≤ 8	7 (15.56)	38 (84.44)	45 (25.71)
9 - 22	8 (18.60)	35 (81.40)	43 (24.57)
23 - 58	2 (4.44)	43 (95.56)	45 (25.71)
≥ 59	3 (7.14)	39 (92.86)	42 (24.00)
Multiple comparisons adjustment			
Yes	6 (10.34)	52 (89.66)	58 (33.14)
No	14 (11.97)	103 (88.03)	117 (66.86)

HTE (heterogeneity of treatment effects) keywords: ‘yes’ if text included the keyword “subgroup”, “heterogeneity”, “interaction”; “modifier”, “stratified”, or “strata” in the appropriate context; otherwise ‘no’

Journal abbreviations: AJODO *American Journal of Orthodontics and Dentofacial Orthopedics*, AO *Angle Orthodontist*, EJO *European Journal of Orthodontics*, KJO *Korean Journal of Orthodontics*, OCR *Orthodontics and Craniofacial Research*

Year = year that article was published in print edition of journal

Continent: continent where ethical approval for study was granted; ‘Asia’ if study was approved in the country of Turkey; ‘Other’ if study was approved in an African or Oceanic country or in two or more different countries

Impact score: ‘low’ if journal’s impact score during the year of RCT publication was less than the median impact score of 1.44 and ‘high’ if journal’s impact score during the year of RCT publication was greater than or equal to the median impact score of 1.44

Study design: ‘other’ if study was crossover design or had multiple designs concurrently, e.g., parallel and split mouth

Entitled RCT: ‘yes’ if title contained the phrase “randomized controlled trial” or “randomized clinical trial”; otherwise ‘no’

Number of subjects randomized: number of individual human subjects randomized

Baseline comparison test: ‘yes’ if statistical test was done to compare baseline characteristics between study groups; otherwise ‘no’

Intention-to-treat analysis: ‘yes’ if authors reported using intention-to-treat analysis; otherwise ‘no’

Number of hypothesis tests: total number of unique hypothesis tests identified in figures and tables of RCT

Multiple comparisons adjustment: ‘yes’ if adjustment for multiple comparisons, such as Bonferroni correction, was reported; otherwise ‘no’

Row (HTE keyword) and column (total) percentages might not add to exactly 100.00 due to rounding

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