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SCIENTIFIC SECTION

Orthodontic Clinical Trials III: Reporting of ethical issues associated with clinical trials published in three orthodontic journals between 1989 and 1998

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Aims: The aims of this study were to assess whether reports of orthodontic clinical trials complied with the requirements of the Declaration of Helsinki.

Design: A retrospective observational study.

Setting: The *American Journal of Orthodontics and Dentofacial Orthopedics* (AJODO), *Journal of Orthodontics* (formerly and up until 1999 known as the *British Journal of Orthodontics*, BJO) and *European Journal of Orthodontics* (EJO).

Data source: Clinical trials published between 1989 and 1998.

Method: A hand search was performed to identify all clinical trials. Each trial report was assessed for inclusion of a statement that ethical approval and/or informed consent had been obtained.

Results: One-hundred-and-fifty-five papers were identified, of which 85 (54.8%) were reports of randomized controlled trials (RCTs) and 70 (45.2%) of controlled clinical trials (CCTs). 16.1% (25/155), of the trial reports stated that ethical approval had been obtained and a quarter (39/155, 25.1%) indicated that informed consent had been obtained.

Conclusions: Most orthodontic clinical trial reports failed to state whether ethical approval and/or informed consent had been obtained. The reporting of the ethical issues associated with orthodontic clinical trials could be improved further not only by the instructions to authors in orthodontic journals stating the need for studies to comply with the Declaration of Helsinki, but also by Journal editors refusing to publish trials that do not comply.

Key words: Clinical orthodontic research, clinical trials, ethical issues, randomized clinical trials, reporting

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Introduction

The Declaration of Helsinki[1] code of ethics on human experimentation, states that the design and performance of experimental procedures involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration and, where appropriate, approval by a specially appointed ethical review committee, which must be independent of the investigator, sponsor or any other kind of undue influence. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, then non-written consent must be formally documented and witnessed.

It is then the responsibility of individual countries as to how these guidelines are applied and implemented. In the UK, there is a system whereby the protocols of all clinical trials are reviewed by the Local Ethics Committees. In the USA a similar system exists and protocols have to be approved by an Institutional Review Board.

If ethical approval for a trial and informed consent from participants have been obtained, then this should ideally be reported in any publication resulting from the

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trial. Compliance with these criteria has been assessed in several studies on reports of research published in a variety of medical journals.[2–11] However, these issues have been neglected in the dental press and no studies could be found that had looked at the inclusion of statements about obtaining ethical approval and/or informed consent in reports of orthodontic, or even, any dental clinical trials.

Aims

The aims of this study were to assess whether reports of orthodontic clinical trials complied with the requirements of the Declaration of Helsinki[1] and test the null-hypotheses that there was no difference in the compliance of reports between those:

1. of controlled clinical trials (CCTs) and randomized controlled trials (RCTs);
2. published in each of the three journals;
3. published between 1989–1993 and 1994–1998.

Method

Identification of clinical trials

The principal investigator successfully completed the Cochrane Collaboration Oral Health Group hand-searching test search for the identification of randomized controlled trials (RCTs) and controlled clinical trials (CCTs).[12] The author then hand-searched the *American Journal of Orthodontics and Dentofacial Orthopedics* (*AJODO*), the *Journal of Orthodontics* (formerly and up until 1999 known as the *British Journal of Orthodontics*, *BJO*) and the *European Journal Orthodontics* (*EJO*) to identify all papers that reported randomized or controlled clinical trials published between 1989 and 1998 inclusive.

Assessments

The ethical issues considered in this study related to obtaining ethical approval for the conduct of the trial and consent from the patients/parents to indicate their willingness to participate in the trial. These criteria were based on compliance with the Declaration of Helsinki.[1] Each trial report was assessed to see whether it reported that it had complied with the ethical requirements of with the Declaration of Helsinki.

Reliability

A random 10% sample of the trials identified in each journal was reclassified to assess the intra-examiner reliability.

Statistical analysis

Descriptive statistics were used to assess the distribution of trials published in the individual journals. The percentage agreement and Kappa statistic[13] were used to assess the intra-examiner reliability of the assessments. Odds ratios and 95% confidence intervals were used to compare whether each of the criteria had been included or not when comparing RCTs and CCTs, and the changes over time. The chi-square test was used to compare the results from each of the three journals.

Results

Between 1989 and 1998, 155 reports of clinical trials were published in the *AJODO*, *BJO* and *EJO*.

Reliability of assessments

The intra-examiner percentage agreement was 100% giving a Kappa statistic of 1.0 (very good agreement) for each criterion.

Ethical issues

One-hundred-and-fifty-five papers were identified of which 85 (54.8%) were reports of randomized controlled trials (RCTs) and 70 (45.2%) of controlled clinical trials (CCTs).

Overall. Sixteen per cent (25/155) of the trial reports stated that ethical approval had been obtained and 25% (39/155) indicated that informed consent from patients and/or parents/guardians had been obtained (see Table 1). A total 70% of reports (108/155) did not include a statement about either ethical approval or informed consent and only 11.0% of reports included statements about both (17/155; see Table 1).

RCTs versus CCTs. No statistically significant difference was found between the proportions of

Table 1 Inclusion of a statement as to whether ethical approval and/or informed consent had been obtained for clinical trials published in *AJODO*, *BJO* and *EJO* 1989–1998

	Informed consent					
	Stated		Not stated		Total	
Ethical approval	%	Number	%	Number	%	Number
Not stated	14	(22)	70	(108)	84	(130)
Stated	11	(17)	5	(8)	16	(25)
Total	25	(39)	75	(116)	100	(155)

reports of RCTs and CCTs that stated that ethical approval had been obtained (OR 1.06, 95% CI 0.45, 2.50). More than twice as many reports of RCTs than CCTs stated that informed consent had been obtained (OR 3.11, 95% CI 1.38, 6.96; see Table 2).

Comparison of journals. No statistically significant differences were found between the proportions of reports published in the *AJODO*, *BJO* or *EJO* that stated that ethical approval had been obtained (Chi square=0.93, df=2, $p>0.05$). Statistically significantly more reports published in the *BJO* and *EJO* stated that informed consent had been obtained (Chi square 25.5, df=2, $p<0.001$; see Table 3).

Changes over time. When considering changes in reporting that had occurred over time, there were improvements in the reporting of whether ethical approval had been obtained (OR 1.92, 95% CI 0.72, 5.12) and stating that informed consent had been obtained (OR 1.33, 95% CI 0.61, 2.88), but these differences were not statistically significant (see Table 4).

Discussion

This study has found that only 11% of trial reports stated that ethical approval for the trial and informed consent from participants in the trial had been obtained. The implications of these findings on the ethics of conducting orthodontic clinical trials will be discussed.

Assessments

Compliance with the ethical issues surrounding the conduct of clinical trials was determined by assessing whether the trial reports stated that ethical approval for the trial and informed consent from the patients/parents had been obtained. The intra-examiner reliability of this assessment was very good. To assess the validity of this assessment authors of the trial reports would need to be contacted to clarify the situation.

Ethical issues

It is over 30 years since the publication of the code of ethics on human experimentation was accepted and published by the World Medical Association[1] so it was disappointing to find that only 16% (25/155) of trial reports examined in this study stated that ethical approval for the trial had been obtained and only 25% (39/155) reported that consent to participate in the trial had been obtained from either the patient or parent/guardian (Table 1). It was also disappointing to find that none of the journals studied stated explicitly, at that time, in their Instructions for Authors that compliance with the Declaration of Helsinki was required for clinical trials.

Table 2 Comparison of whether reports of CCTs and RCTs included a statement of whether ethical approval and/or informed consent had been obtained for clinical trials published in *AJODO*, *BJO* and *EJO* 1989–1998

	Ethical approval						Informed consent					
	Stated		Not stated		Total		Stated		Not stated		Total	
	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number
CCT	16	(11)	84	(59)	100	(70)	14	(10)	86	(60)	100	(70)
RCT	17	(14)	83	(71)	100	(85)	34	(29)	66	(56)	100	(85)
Total	16	(25)	84	(130)	100	(155)	25	(39)	75	(116)	100	(155)

Table 3 Comparison of whether reports of clinical trials published in *AJODO*, *BJO* and *EJO* between 1989 and 1998 included a statement of whether ethical approval and/or informed consent had been obtained

	Ethical approval						Informed consent					
	Stated		Not stated		Total		Stated		Not stated		Total	
Journal	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number
AJODO	14	(14)	86	(85)	100	(99)	12	(12)	88	(87)	100	(99)
BJO	22	(4)	78	(14)	100	(18)	56	(10)	44	(8)	100	(18)
EJO	18	(7)	82	(31)	100	(38)	45	(17)	55	(21)	100	(38)
Total	16	(25)	84	(130)	100	(155)	25	(39)	75	(116)	100	(155)

Surprisingly, there was no statistical difference between the proportions of reports of RCTs and CCTs that stated that ethical approval had been obtained (OR 1.1, 95% CI 0.4, 2.5) despite more than twice as many reports of RCTs than of CCTs stating that informed consent had been obtained (OR 3.1, 95% CI 1.38, 6.96). There were improvements over time in the reporting of whether ethical approval (OR 1.92, 95% CI 0.72, 5.12) and informed consent (OR 1.33, 95% CI 0.61, 2.88) had been obtained, but these were not statistically significant. This may be a reflection of type II error due to the number of reports and consequent wide confidence intervals.

Comment has been made that the failure to state that ethical approval and/or informed consent had been obtained in clinical trials was an oversight by authors.[14] Alternatively, it could be suggested that if researchers go to the time and trouble of obtaining ethical approval and consent for a trial then they would want to report the fact in the trial report. There is also a responsibility on referees and Journal editors to ensure that ethical requirements are adhered to.

The need to indicate whether the procedures followed were in accordance with ethical standards of the responsible committee on human experimentation and the Declaration of Helsinki[1] is stated in the guidelines produced by the International Committee of Medical Journal Editors.[15] This requirement is maintained in the Asilomar Working Group recommendation for reporting clinical trials.[16] However, it is disappointing that this requirement has not been included in the CONSORT statement,[17] which aims to improve the quality of reporting of RCTs. Justification for omission of this requirement is that, when developing the original CONSORT statement, the intention of the authors was to keep only those items deemed fundamental to reporting standards for an RCT and those that would have an effect on its validity. The authors considered that there were some items that were not considered as essential, e.g. ethical approval, that it may well be highly desirable to include and should still be included in an RCT report even though they are not specified as necessary in CONSORT.[18]

In a review of the Instructions for Authors of 192 medical journals less than half (48/102, 47%) required Institutional Review Board (IRB) approval of studies involving human participants as a prerequisite for publication and in a quarter of journals no guidelines were given.[19] The review also found that the other journals either referred authors to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals,[15] the Declaration of Helsinki[1] or indicated that informed consent should be obtained.

Comparison with other studies. Several similar studies have been carried out on reports of research published in a variety of medical journals.[2–11] The results of these studies are summarized in Table 5. In all these studies, the level of reporting of whether ethical approval and/or informed consent had been obtained was higher than in the three orthodontic journals examined in this study. In studies that have differentiated between clinical trials and other methods of research, the level of reporting was found to be much higher for RCTs than other methods. This study found similar results for the reporting of whether informed consent had been obtained, but not for ethical approval. One of the most notable findings was that for studies examining RCTs involving children the level of reporting of whether ethical approval had been obtained was six times as frequent as for the orthodontic clinical trials investigated in this study, which probably involve mainly children and adolescents.

Generalizability

The papers examined in this study were published in three journals between 1989 and 1998. From these respects the results may not be generalizable to other orthodontic journals or dental journals, and may not reflect current publishing practice. However, plans have been made to update and broaden this study to include trials published more recently and in journals of other dental specialties.

Table 4 Comparison of whether reports of clinical trials published in *AJODO*, *BJO* and *EJO* between 1989–1993 and 1994–1998 included a statement of whether ethical approval and/or informed consent had been obtained

	Ethical approval						Informed consent					
	Stated		Not stated		Total		Stated		Not stated		Total	
	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number
1989–93	11	(6)	89	(49)	100	(55)	22	(12)	78	(43)	100	(55)
1994–98	19	(19)	81	(81)	100	(100)	27	(27)	73	(73)	100	(100)
Total	16	(25)	84	(130)	100	(155)	25	(39)	75	(116)	100	(155)

Table 5 Other studies assessing whether a statement of whether ethical approval and/or informed consent had been obtained was included in the published report

First author	Year	Journal(s)/specialty year(s) examined	Data sources	Ethical approval	Informed consent (IC)
Olson[1]	1996	Cardiopulmonary resuscitation	47 studies	51% mentioned approval by research ethics committee (REC)	26% addressed the issue of IC
Olde Rikkert[3]	1996	Geriatrics 1993–1994	37 clinical trials	49% mentioned approval by REC	62% reported that IC was obtained
Karlawish[4]	1999	Nursing home care	45 studies	45% reported Institutional Review Board (IRB) review	80% reported that IC was obtained
Matot[5]	1998	Critical care medicine	279 studies	No evidence of IRB review and IC in 24% of studies. IRB approval, but IC not mentioned in 13% of studies	
Ruiz-Canela[6]	1999	*N Engl J Med*, *Lancet*, *JAMA*, *BMJ* 1993–1996	767 clinical trials	71% reported REC approval	80% reported that IC was obtained
Ruiz-Canela[7]	2001			64% reported both REC approval and IC	
Bauchner[8]	2001	Pediatric studies in *JAMA*, *N Engl J Med*, *Pediatrics*, *J Pediat*, *Arch Pediat Adol Med* 1999	561 studies	61% reported REC approval	Not examined
			86 RCTs	97% reported REC approval	Not examined
Weil[9]	2002	*Paediatrics*	379 studies	52% documented IRB approval. 35% documented IRB approval and IC	43% documented IC was obtained
Yank[10]	2002	*Annl Int Med*, *BMJ*, *JAMA*, *Lancet*, *N Engl J Med*, July 1995–June 1997 *v.* July 1997–June 1999	600 clinical trials	Pre-1997 31% did not report REC approval	26% did not report IC
				Post-1997 18% did not report REC approval ($p=0.01$)	18% did not report IC ($p<0.001$)
Myles[11]	2003	*Anaesthetics* 2001	1189 studies	71% documented REC approval	66% documented IC

With respect to the time frame of the study it appeared that the reporting of these ethical issues was improving and it would have been hoped that by now publication of trials without ethical approval and/or informed consent from participants would not be occurring. However, as reported in a recent Editorial[20] in the *Journal*, papers are still being submitted for publication without (apparently) having been subjected to ethical approval or having gained consent from participants. It is pleasing to note though that the Editor is taking the lead in rejecting such studies in accordance with the *Journal's* current Instructions for Authors.

Implications of the reporting of ethical issues on orthodontic clinical trials

Adherence or not to ethical guidelines may not have any impact on the outcome of a clinical trial and conclusions of any systematic review it is included in, but it may be an indication that the right of the participants in the trial have not been respected. This is something that has become a national issue in the UK.[21,22] In addition, if ethical approval has not been sought, then it raises questions as to whether a trial would have received permission to proceed.

If we, as a profession, want to protect our patients who participate in orthodontic clinical trials, most of whom are children and adolescents, we need to ensure that our clinical trials are of the highest ethical standards, regardless of the age of the patient. To encourage correct procedures, journals' instructions for authors could not only state that trials seeking publication need to comply with the Declaration of Helsinki,[1] but also take steps to try and encourage compliance. For example, whilst non-compliance may not prevent unscrupulous researchers from conducting trials, if they are not published it will ensure that the reports that are published are of trials that respect the rights of the participants by informing them of the trial and requesting their permission to participate in the trial. Hopefully, if journals request evidence of a trial's compliance with the Declaration of Helsinki, then researchers, who will eventually seek to publish their work, will ensure that the trial meets the necessary requirements at the outset of the trial, rather than run the risk of not being able to have any reports of the trial published in a peer reviewed journal.

Conclusions

The reporting of whether ethical approval for the clinical trial and/or informed consent had been obtained from participants in orthodontic clinical trials published in *AJODO*, *BJO* and *EJO* between 1989 and 1998 was inadequate. This raises concerns about the ethical conduct of orthodontic clinical trials.

Recommendations

Special attention needs to be drawn to the ethical issues surrounding the conduct of clinical trials with special reference to the need to get and report that ethical approval for the trial and informed consent from participants has been obtained.

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Contributors

Jayne Harrison was responsible for the conception and design of the study, writing of the protocol, material and data collection, data analysis, and interpretation and writing of the article. Professor Ashby assisted in the design of the study, data analysis and interpretation, reviewed and commented on the write up of the work that contributed to this article. Professor Lennon assisted in the design of the study, and reviewed and commented on the write up of the work that contributed to this article. Jayne Harrison is the guarantor.

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