The Reporting of Ethical Approval and Informed Consent for Clinical Trials in Four Major Orthodontic Journals.

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Abstract

Background:

All research involving human participants should have ethical approval and informed consent. There is no recent evidence on the incidence of reporting of compliance with these ethical criteria in orthodontic journals, nor is there evidence on which factors predict the compliance of Randomised Controlled Trials (RCTs) with ethical approval and informed consent.

Aims:

This study aimed to:

- Assess the number of Randomised Controlled Trials and Controlled Clinical Trials (CCTs) published in the American Journal of Orthodontics and Dentofacial Orthopedics, Angle Orthodontist, European Orthodontic Journal and Journal of Orthodontics (formerly British Journal of Orthodontics) between 1st January 2001 and 31st December 2010.
- Determine the number of these papers which recorded having obtained ethical approval and informed consent.
- Determine the number of authors, number of centres, location, involvement of a statistician, year of publication and the presence of "random*" in either the title or abstract or body of the RCTs.
- Determine whether the factors above influenced an RCT's likelihood of having recorded ethical approval and informed consent.

- Determine the sensitivity of identifying RCTs in the four journals under consideration using various electronic search methods, through a MEDLINE search via PubMed and Ovid, for publication type "RCT" and PubMed free text search for "random* AND orthodontic". Compare results with previously published findings.

- Compare the electronic search methods with handsearching as the gold standard.

Design:

Retrospective observational study.

Data Sources:

Articles published between 1st January 2001 and 31st December 2010 in the American Journal of Orthodontics and Dentofacial Orthopedics (AJODO), The Angle Orthodontist (AO), European Journal of Orthodontics (EJO) and Journal of Orthodontics (JO) (formerly British Journal of Orthodontics).

Sample:

All CCTs and RCTs published in the AJODO, AO, EJO and JO between 1st January 2001 and 31st December 2010 were included.

Method:

- RF passed the Cochrane Oral Health Group Handsearching test.

- A search of all CCTs and RCTs published in the AJODO, AO, EJO and JO between 1st January 2001 and 31st December 2010 was performed.

- The RCTs and CCTs were assessed for a statement that the paper had obtained ethical approval and informed consent.

- The RCTs were further analysed to determine the following criteria: publication journal, number of authors, number of centres, location of origin, involvement of a statistician, year of publication, and whether random* was in the title or abstract or body of the article.

Results:

Over the ten year period 4748 articles were identified, of which 218 reported RCTs and 89 CCTs. RCTs comprised 4.6% and CCTs 1.9% of all articles published over that time period. Of the CCTs, 36% had reported both ethical approval and informed consent and 39.3% had neither. Of the RCTs, 48.6% had reported both ethical approval and informed consent and 27.1% had neither.

Factors associated with an RCT reporting that ethical approval and informed consent had been obtained were:

Number of authors ($p<0.001$), Random* in Title ($p<0.001$), Random* in Abstract not Title ($p<0.001$), Location of origin ($p=0.001$), Year of publication ($p=0.003$), The journal of publication ($p=0.004$) and Number of centres ($p=0.008$).

A logistic regression analysis showed that the most significant indicators of ethical approval and informed consent having been reported were:

Publication in the JO ($p=0.018$), 6 or more authors ($p<0.001$), Random* in the abstract not title ($p=0.004$) and Publication after 2004 ($p=0.001$).

A comparison of handsearching with three commonly used electronic search methods showed that handsearching was more accurate. Ovid was significantly less sensitive than PubMed (OR 8.43, 95% CI 5.48, 12.97) missing 157 RCTs (72.0%), while PubMed missed 51 (23.4%). The free text PubMed search, using the terms orthodontic AND random*, was the most sensitive missing 45 RCTs (20.6%); though this was not statistically significant (OR 0.85, 95% CI 0.54, 1.34)

Only 56 RCTs (25.7%) were found by all 3 electronic searches. However 37 RCTs (17%) were not identified by any of the electronic search strategies.

Conclusions:

The reporting of whether ethical approval and informed consent had been obtained are inadequately reported in papers reporting orthodontic RCTs and CCTs. RCTs published in the JO, those with 6 or more authors, with Random* in the abstract but not the title and those published after 2004, were most likely to have reported that ethical approval and informed consent had been obtained. Handsearching was more accurate than electronic searching and PubMed more sensitive than Ovid.

Chapter 1: Introduction

Research ethics are regarded as 'the more or less deliberate and systematic consideration of moral problems arising in connection with the conduct and consequences of scientific research'.[1] Ethical approval and informed consent are essential aspects of any research involving human subjects, as they are concerned with the most basic of human rights, namely the right to life, liberty and security of person, together with freedom from inhuman and degrading treatment[2] (Articles 3 and 5 of United Nations' Declaration of Human Rights). Scientific research embodies these concepts in the code of ethics on human experimentation known as the Declaration of Helsinki.[3]

Previous orthodontic research by Harrison[4] indicated a low level of compliance with both ethical approval and informed consent for both orthodontic RCTs and CCTs. In this thesis I examined orthodontic Controlled Clinical Trials (CCTs) and Randomised Controlled Trials (RCTs), published over the past ten years in the American Journal of Orthodontics and Dentofacial Orthopedics (AJODO), the Angle Orthodontist (AO), the European Journal of Orthodontics (EJO) and the Journal of Orthodontics (JO), (formerly the British Journal of Orthodontics (BJO)) and evaluated whether the RCTs and CCTs published in these journals fulfill the criteria specified by the Declaration of Helsinki, namely having obtained ethical approval and informed consent. I also investigated the RCTs further to identify predictors of satisfying ethical criteria. These predictors included the number of authors and research centres involved, any use of a statistician, year of publication and the country of origin of the study.

In this era of Evidence Based Medicine (EBM), clinical decisions increasingly require a strong basis in, and support from, scientific evidence. The pinnacle of evidence is considered

to be a meta-analysis of RCTs.[5] These meta-analyses require the identification and consideration of all relevant studies for potential inclusion so as to reduce inter-trial bias. Published guidelines on meta-analyses identify a common search strategy, most often that developed for MEDLINE or a revision of same; such strategems often involve a combination of controlled vocabulary and free text terms.[6] In addition, in this thesis I will assess the efficiency of locating RCTs on MEDLINE using various search methods and compare this to the gold standard of handsearching.

Chapter 2: Literature Review

Principles of Ethics

There are four principles of biomedical ethics:

1. **'Primum non nocere'** (first do no harm), is also known as non-malificence, as included in the Hippocratic Oath.[7]

2. **Beneficence** – acting in a positive fashion, to improve a situation and in the best interests of your patients.

3. **Justice** – all patients should be treated equally with fair apportioning of resources.

4. **Autonomy** – the right of an individual to make informed decisions for themselves without pressure, according to their capacity.

Dignity and honesty are also important ethical principles.

Such ethical principles are obviously central to the provision of healthcare as well as research. Topical issues such as just allocation of expensive treatment on a background of a dearth of resources (the so-called "Postcode Lottery"), requests for voluntary euthanasia and the use of tissue from aborted foetuses, all pose ethical dilemmas which are examined through the medium of the four principles mentioned above. Many ethical questions in our clinical practice can only be answered by well performed and ethical research bearing in mind such mandates. Orthodontic research aims to develop and test effective, reliable and robust clinical treatments, therefore questions such as: "should treatment be provided early or late?", "should it be delivered in one or two phases?", "can functional appliances modify growth?", can best be answered by well designed and ethical research.

What is research?

Research is defined as "the attempt to derive generalisable new knowledge, including studies that aim to generate hypotheses as well as studies that aim to test them".[8] It is thus different from both clinical audit and service evaluation. These are defined respectively as being "designed and conducted to produce information to inform delivery of best care"[8] and "designed and conducted solely to define or judge current care".[8]

Each country has their own guidelines as to when ethical approval and informed consent are required.[9, 10] European Union guidelines are common to all member states.

Ethical Guidelines: History and the Law

Contemporary research is strictly governed by several guidelines (Table 1.1), chief amongst which is the Declaration of Helsinki (DoH), promulgated by the World Medical Association (WMA).[3]

Table 1.1 Guidelines concerning the Protection of Human Participants.

Nuremberg Code. [11]
Declaration of Helsinki – World Medical Association.[12]
International Ethical Guidelines for Biomedical Research involving Human Subjects – Council for International Organisations of Medical Sciences and the World Health Organisation.[13]
Universal Declaration on Bioethics and Human Rights – United Nations Educational Scientific and Cultural Organisation.[14]
Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine – Convention on Human Rights and Biomedicine, Council of Europe.[15]
Uniform Requirements for Manuscripts to Biomedical Journals – International Committee of Medical Journal Editors.[16]
Recommendations on Publication Ethics Policies for Medical Journals. – World Association of Medical Editors. [17]
Medical Research Guidelines- Human Tissue and Biological Samples for use in Research-Operational and Ethical Guidelines.-Medical Research Council.[18]
Code of Conduct and Best Practice Guidelines for Journal Editors. – Committee on Publication Ethics (COPE) Council.[19]
CONSORT (Consolidated Standards of Reporting Trials) statement for reporting of RCTs – CONSORT Group.[20]
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) – PRISMA Group.[21]

These guidelines are issued by a number of authorities, from those involved in publishing, for example CONSORT and PRISMA, to International and National organisations. International organisation such as the UN's Universal Declaration on Bioethics and Human Rights and World Medical Association's Declaration of Helsinki. National organisations include the UK's Medical Research Council's Operational and Ethical Guidelines. The International

Committee of Medical Journal Editors' (ICJME's) uniform requirements for manuscripts submitted to biomedical journals require that,

> *"authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration. If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the Study".*[16]

Nearly 900 journals state that they have adopted the ICJME's requirements.[22] These guidelines all attempt to protect human subjects' rights and autonomy, maintain ethical standards and ensure the integrity of biomedical research on human participants. The requirements of the Declaration of Helsinki must be fulfilled when carrying out such research.

An ethical attitude towards evidence-based research is not a modern phenomenon. Avicenna (Ibn Sîna, c. 980 – 1037) was one of the first to discuss concepts of ethical research and RCTs.[23] His *Canon in Medicine* (*Al-Qanun fil-Tib)* explored the concepts of evidence-based medicine including RCTs.[24]

In the early twentieth century, codes of ethics for research and the treatment of human subjects were introduced in countries such as Germany (1931)[25] and the Soviet Union (1936).[26] However, the main stimulus towards the development of a comprehensive statement of moral duties and ethical requirements in research was as a direct result of several infamous experiments performed in a variety of nations during the first half of the twentieth century.

This included Japan's Unit 731, Australian mustard gas experimentation, human radiation trials, the Tuskegee Syphilis Study and Nazi Germany's notorious experiments in the concentration camps.[7] Dentistry moreover, is not immune from participation in unethical trials, The Vipeholm experiments, for example, involved the subjection of mentally handicapped subjects to large volumes of sugar so as to induce an experimental human model of caries.[27, 28]

The public airing of such heinous experiments helped provide an impetus towards the conceptualisation of the "dignity" of the human body and its existence. This tenet became more closely defined with reference to the Medical Sciences and research ethics, taking a central role in the international reaction to the atrocities of World War Two. The Universal Declaration of Human Rights (1948)[29] and International Covenant on Civil and Political Rights (1966)[2] both employ the term "dignity" as defining the status of humans,[30] something rather different from the traditional English meaning of the term. Following the Latin word *Dignitas*, dignity referred to rank in society, honour and importance, as in the famous Shakespeare prologue,

> *"Two households, both alike in dignity,*
>
> *In fair Verona, where we lay our scene..."*[31]

Contemporary understanding of a "dignity" of the human state was deeply influenced by the stance of the 18th century philosopher Immanuel Kant, who differentiated between dignity and price, or absolute and relative value:

> *"In the kingdom of ends everything has either a price or a dignity. Whatever has a price can be replaced by something else as its equivalent; on the other hand, what is above all price, and therefore admits of no equivalent, has a dignity."*[32]

Thus a human being is intrinsically priceless and therefore has dignity but no price, in contrast to an inanimate object which has a price but no dignity.

This moral conceptualisation has led bioethicists throughout the twentieth and twenty first centuries to consider the human body as the locus of absolute dignity. Thus, this dignity involves the protection and preservation of its integrity, with dignity being destroyed if any part of the body is assigned a monetary value and thus rendered alienable and transferable. For example, participation in clinical trials or organ donation for financial gain.

Direct payment for human tissue, blood, organs and suchlike is not permissible in Western Europe and some of the Industrialised Commonwealth countries (Canada, Australia, New Zealand); the human tissue must be donated.[33, 34] Sperm donation is an exception to this rule, where donors are often paid "expenses". A recent recommendation made by the Nuffield Council on Bioethics proposed a pilot scheme in which the funeral expenses of organ donors are paid for by the NHS.[35] If this were to be successful it may be a more ethical method of encouraging an increase in subscription to the Organ Donation Register. Paying for the funeral expenses would be ethical as no harm would come to the donor and it would be a form of recognition of such a sacrifice from society, further reinforcing the value of these voluntary donations. Currently the organ donation requests of approximately 10% of organ donors are rejected by their families at the time of death; such recognition may perhaps reduce this number. Unlike most other parts of the world, in the USA it is permissible to sell

blood, creating a mixture of voluntary and paid blood collection services. There is evidence that blood from paid donors has a higher risk of being infected than that provided by donors gratis, as the motivation for giving blood is different and less likely to be given for purely altruistic reasons.[36, 37]

Introduction of the Nuremberg Code and Development of the Declaration of Helsinki

The Nuremberg Code was introduced in 1947 as part of the Nuremberg Trials which comprised part of a series of military tribunals, held by the Allied Forces at the end of World War II. These trials were presided over by a cohort of judges from the victorious Allied powers, British, French, USA and Soviet Union and passed judgement on major Axis political, economic and military figures who were accused of war crimes including Speer, Donitz and Goering amongst others. Those doctors who had been accused of torturous and murderous human experimentation in the concentration camps were also tried in separate proceedings.[38] The primary ideology of the doctors' trials was that although these were murder trials, they also considered the role of "Hippocratic" values and ethics, holding up the role of the Medical Professional as one who implicitly abides by the concept of the "Hippocratic Oath" and "Primum Non Nocere".[39] As a result of the judgement against these doctors, the Nuremberg Code was introduced. This enshrined twelve principles, including informed voluntary consent, that the participant was at liberty to end his/her role in the experiment at will and that the experiment be carried out in such a way as to avoid all unnecessary physical and mental suffering and injury.[7, 40] The requirement of informed consent has been accepted worldwide and is articulated in international law in Article 7 of the United Nations International Convention on Civil and Political Rights (1966).[2, 41] In 1947 the newly formed World Medical Association (WMA) endorsed a modernized version of the

Hippocratic Oath.[25] Then in 1954, the WMA adopted the Resolution on Human Experimentation. Following on from this, the Declaration of Helsinki (DoH) was developed by the World Medical Association (WMA) in 1964. The DoH developed ten of the twelve ethical principles of the Nuremberg Code and allied them to the Declaration of Geneva, thus specifically addressing clinical research.[42] One of the two areas which were more clearly defined in the transfer from the Nuremberg Code to the Declaration of Helsinki was that of informed consent. The Nuremberg Code states that: *"the voluntary consent of the human subject is absolutely essential"*, this is different to the Declaration of Helsinki, where consent can be given by a "legal guardian" in case of "legal incapacity" (Article II.1). The following sentence was removed in the transition from the Nuremberg Code to the Declaration of Helsinki,

> *'During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible'*.[38]

This was replaced with a somewhat similar statement in the Declaration of Helsinki, that the participant has the freedom to opt out of the experiment at any time and the investigator must *"discontinue the research if in his or their judgement it may, if continued, be harmful to the individual"*.[12]

Since it was enacted in Helsinki in 1964, the Declaration has been regarded as "the most widely accepted guidance worldwide on medical research involving human subjects."[43] Although the Declaration is not a legally binding document; it draws its authority from the degree into which it has influenced national legislation. Humans and Fluss referred to the importance of this document,

"*Even though the Declaration of Helsinki is the responsibility of the World Medical Association, the document should be considered the property of all humanity*".[44]

The Declaration of Helsinki has since undergone six revisions, most recently in 2008, including "independent committees" (Article I.2) to oversee the implementation of the Declaration, which subsequently developed into research ethics committees.

When is ethical approval required?

The requirement for ethical approval varies from country to country. In the European Union (EU) and United States of America (USA) ethical approval is required from an ethics board for all research involving humans or animals, as is the case for most countries. However in Canada, a research ethics board review is only required if the research is funded by an organisation which requires ethical review, for example, a University or in the case of clinical trials on experimental drugs. If the researcher is able to obtain funds through other methods it is possible to avoid the ethical review board.[45]

In the United Kingdom (UK), the National Research Ethics Service (NRES formerly COREC) has overall responsibility for determining that ethical approval is obtained for that research which requires it and that a log is kept of all research involving human participants.[46]

Ethical approval in the UK must be obtained for any research involving humans, encompassing the testing of new interventions on participants, research on human tissue and the review of personal data such as radiographs.[10]

Ethical REVIEW is necessary for research in many situations:[46]

1. *" Potential research participants identified from, or because of, their past or*

present use of the services...(including services provided under contract with the private or voluntary sectors), including participants recruited through these services as healthy controls;

2. *Potential research participants identified because of their status as relatives or carers of past or present users of these services;*
3. *Collection of tissue (i.e. any material consisting of or including human cells) or information from users of these services; or*
4. *Use of previously collected tissue or information from which individual past or present users of these services could be identified, either directly from that tissue or information, or from its combination with other tissue or information in, or likely to come into, the possession of someone to whom the tissue or information is made available."*
5. *"Xenotransplantation (i.e. putting living cells, tissue or organs from animals into people), which, as a matter of Government policy, is recommended to take place in a controlled research context, carried out with a research protocol approved by a REC within the UK Health Departments' Research Ethics Service;*
6. *Health-related research involving prisoners, for which the National Offender Management Service, Scottish Prison Service and Northern Ireland Prison Service require review by a REC as well as compliance with their own approval procedures;*

7. *Social care research projects funded by the Department of Health, which must always be reviewed by a REC within the Research Ethics Service for England".*

Informed Consent

Informed consent is required from all human participants, including when their data or tissues are being utilised, as required by the Declaration of Helsinki. As mentioned previously, consent is to be obtained personally if at all possible but it is acceptable for consent to be given by proxy in specific circumstances.

For participants in clinical trials there are statutory requirements for their informed consent. These regulations are set out in Schedule 1 of the Medicines for Human Use (Clinical Trials Regulations) 2004.[47] These regulations transposed the European Clinical Trials Directive (EC2001/20)[48] into UK law. The European Clinical Trials Directive gives clear guidance concerning informed consent:

"A person gives informed consent to take part in a clinical trial only if his decision:

a. *Is given freely after that person is informed of the nature, significance, implications and risks of the trial.*

and

b. *Either:*

(i) *Is evidenced in writing, dated and signed, or otherwise marked, by that person so as to indicate his consent.*

Or:

(ii) If the person is unable to sign or to mark a document so as to indicate his consent, is given orally in the presence of at least one witness and recorded in writing."[47] *(Paragraph 3(1))*

The same definition applies whenever informed consent is given, whether by a person with parental responsibility or a legal representative, on behalf of the trial subject.

Informed consent in adults with capacity also requires further conditions to be met:

1. *"The subject has had an interview with the investigator, or another member of the investigating team, in which he has been given the opportunity to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted.*
2. *The subject has been informed of his right to withdraw from the trial at any time.*
3. *The subject has given his informed consent to taking part in the trial.*
4. *The subject may, without being subject to any resulting detriment, withdraw from the clinical trial at any time by revoking his informed consent.*
5. *The subject has been provided with a contact point where he may obtain further information about the trial".*[47] *(Part 3)*

These EU policies operate in conjunction with UK Department of Health guidelines. First issued in 1964, these guidelines outlined rigorous consent procedures and have subsequently undergone numerous revisions, most recently in October 2000. Furthermore, these guidelines have been supplemented by another publication in 2001, the Research Governance

Framework for Health and Social Care. This explicitly places informed consent at the heart of ethical research and requires the review of research by ethics committees.

For consent to be valid it must be freely given and informed. The Declaration of Helsinki states the importance of adequate information about the investigation (Article 22) and the importance of voluntariness (Article 23). The amount of information disclosed to participants must pass the "reasonable person" test. This concept of the amount of information a "reasonable person" would require to give informed consent originated as a result of a Canadian Supreme Court case – *Halushka versus University of Saskatchewan.*[49] In this case, Walter Halushka was a participant in a trial who consented to have an arterial catheter inserted under general anaesthetic. He was not informed that he might be exposed to unknown risks, nor was he advised that the anaesthetic drug being tested was experimental and had never been tested previously. Furthermore, although he was advised that a catheter would be inserted into an artery in his arm, he was not informed that this catheter would then be advanced into his heart. The anaesthetic was administered through the catheter directly into his heart, which unfortunately resulted in a cardiac arrest. It took approximately 90 seconds for his chest to be opened so manual heart massage could be performed. Despite successful resuscitation, he suffered a degree of hypoxic brain injury, with subsequent mental impairment. In giving his summative assessment, the presiding judge, Justice Hall, stated that:

> *"In my opinion the duty imposed upon those engaged in medical research. . . To those who offer themselves as subject for experimentation . . . Is at least as, if not greater than, the duty owed by the ordinary physician or surgeon to his patient. There can be no exceptions to the ordinary requirement of disclosure in the case of research as there may well be in ordinary medical practice . . . . The example of risks*

> *being properly hidden from a patient when it is important that he should not worry can have no application in the field of research. The subject of medical experimentation is entitled to a full and frank disclosure of all the facts, probabilities and opinions which a reasonable man might be expected to consider before giving his consent."*[49] (supra note 6 at 436)

Thus, the researcher must give full and frank disclosure of all risks, rather than the usual assessment of balance of risk between probable effects of new treatment versus lack of treatment. Justice Hall felt that all the risks that a "reasonable person" would wish to know must be raised and explained before enrolment.[50] By settling the level of disclosure at that that a "reasonable person" would expect Justice Hall implicitly disregarded the option of therapeutic privilege as a justification for a lack of "full and frank disclosure". Therapeutic privilege being the legal doctrine which permits medical professionals to withhold information from their patients if it is deemed in the patient's best interest to do so.[51]

The amount of information disclosed must also be relevant to the individual person in their individual situation. This point was introduced in the *Reibl versus Hughes* case, another Canadian case which was heard in the Canadian Supreme Court in 1980.[52]
In this case a Mr Reibl, then 44 years old, underwent surgery to remove an occlusion in his left internal carotid artery. The surgery was competently performed by a Mr Hughes, the surgeon. However Mr Reibl suffered a major stroke either during the operation or immediately post-operatively. This resulted in paralysis affecting the left side of his body and impotency. Although he had formally consented to the operation, he claimed afterwards that he was not fully informed of the risks involved and therefore that his consent was not valid. This was as Mr Hughes, the surgeon, had only discussed with the patient the risk of a

stroke if the surgery was not performed and had not informed him of the risk of stroke as a result of the operation. Mr Reibl was, at the time of his operation, eighteen months away from fulfilling the minimum eligibility criteria for a lifetime retirement pension and extended disability benefits from his employer. He claimed that he would not have proceeded with the surgery had he known there was even a minimal risk associated with the procedure or at the very least he would have delayed the surgery, as his was not an emergency case, until he had received his full pension and disability benefits. His legal team argued that this was not valid consent as he was not fully informed of all the risks. The importance of the "reasonable person" test was summarised by the presiding judge, Judge Laskin:

> *"What the doctor knows or should know that the particular patient deems relevant to a decision whether to undergo prescribed treatment goes equally to his duty of disclosure as do the material risks recognized as a matter of required medical knowledge. . . . To allow expert medical evidence to determine what risks are material, and hence, should be disclosed and, correlatively, what risks are not material is to hand over to the medical profession the entire question of the scope of the duty of disclosure, including the question whether there has been a breach of that duty"*[52] (supra note 5 at 12-13)

The concept of individuals giving informed consent, having received all relevant information pertinent to their individual situation, creates difficulties in designing consent forms for clinical trials. Research consent forms are generally written for the entire group of participants rather than each individual. Thus in order to provide all the information which is pertinent to each individual participant, at that point in time, a large amount of information must be included in the consent documents. Consent documents have therefore increased in

length over time.[53] Although participants are now provided with more information, this has not lead to increasing levels of knowledge.[54] Understandable information contributes to increasing comprehension but only up to a certain optimal level.[55] Thus, although strict levels of information disclosure means a greater volume of information is provided, [53] this increased volume of information does not result in a greater level of understanding beyond that certain optimum level for each person.

Another problem with consent forms is their readability. It is accepted that research documents should be written at level which would be understood by a thirteen to fourteen year old.[56] However, this is generally not the case. The vast majority of these consent forms are written at a literary level which exceeds the comprehension level of the general population.[57] These overly technical and complicated consent forms may well simply frustrate the potential participant, either in terms of excessive length or complexity, leading to inappropriately given or withheld consent, including the signing of documents that participants have not actually read.[58] Another development, complicating the readability of these consent forms is their use as legal tools by sponsoring companies, in order to demonstrate that they have consented for all possible risks.[59]

Differing formats can have an effect on the readability of consent forms.[57] Recent research in paediatric anaesthetics has demonstrated that using a more visual format, especially pictograms,[60] leads to parents being better informed when consenting their children for research than those parents consented using text alone.[61] Graphical presentation of risks and benefits are particularly beneficial in individuals with low numeracy at enhancing understanding and therefore improving informed consent.[62]

The right to autonomy is a central tenet of the Universal Declaration of Human Rights so that a sufficiently rational and mature patient may accept or reject medical treatment even if it would be pejorative to their own health; a Jehovah's Witness may refuse a blood transfusion although such a course of action may result in their death. In UK law, any treatment without consent is assault known as the crime of Battery in UK law, as well as opening the culprit up to the civil tort of negligence. Two of the "Lords of Appeal in Ordinary", chief justices in the House of Lords, in *Chester v Afshar* declared that a patient's rights to autonomy and dignity must be accorded the highest priority by UK law[63] (at paras 17 and 24). Lord Steyn stated that in *"....modern law, paternalism no longer rules"*[63] (at para 16). However, in the UK, the onus of proof lies with the patient to prove that they did not consent to treatment.[64]

Consent in Specific Circumstances

A significant proportion of orthodontic research has focused on children, legally referred to as minors. There are specified consent procedures for both minors and "incapacitated adults", namely adults who are unable to consent for themselves. These groups are specifically protected by the European Clinical Trials Directive and should not be included in trials if the same results could be obtained by using people capable of giving consent.[48]

Yet there is a need for clinical trials involving children. Children have developmental, physiological and psychological differences from adults and therefore age- and developmental-related research is important for their benefit. Thus, it is important that research is carried out on medicinal products that may benefit children, for example vaccinations and orthodontic appliances which are generally provided in childhood and adolescence. Child specific research on drugs is also important to ensure that the drugs have

been appropriate tested and licenced for use in children. In 2003 the National Audit Office reported that up to 90 per cent of medicines prescribed to children in hospital were not licenced for that use.[65] The EU introduced legislation in 2006 to help remedy this and ensure more drugs are tested and authorised for use in children.[66] However the market for paediatric drugs is small and long-term follow-up of adverse effects is often required as the risks associated with paediatric treatments are generally higher.[67]

As regards other groups incapable of giving consent for participation in studies of this nature, for example certain psychiatric patients or those suffering from advanced dementia, inclusion in clinical trials is even more restrictive. In this situation, the medicinal products on trial should only be administered where there are grounds for assuming that the product will give the participant a direct benefit and outweigh the risks involved. Generally, the participant's legal guardian will need to provide written consent, in co-operation with the participant's treating doctor, before participation in any trial.[68]

Research ethics committees (RECs) have a specific statutory responsibility towards minors and incapacitated adults and must have a member with suitable expertise in these areas. If they do not, then advice must be obtained on the clinical, ethical and psychosocial problems that may arise through this trial.[69]

With regards to an incapacitated adult, the REC must have a member with professional expertise in both the treatment of the disease the trial relates to and also the treatment of the disease the participant is suffering from. If such a member is not part of the REC then it again must obtain advice on the clinical, ethical and psychosocial problems that may result as a consequence of the trial. There are specific procedures laid out for consulting such expert referees.[69]

Consent and Minors

When consenting for research, the Medicines for Human Use (Clinical Trials) Regulations 2004, applicable in England, Wales and Northern Ireland, define a minor as someone under the age of 16 years.[47] When common law applies- all situations not covered by the Regulations- the law states that the age of majority is 18 years.[70] However, whilst not considered to have fully reached adulthood, young people between the ages of 16 and 18 years are assumed competent to give consent. No statute governs the rights of those under 16 years to give consent for medical treatment or research.

These regulations classify a minor as being a person under the age of 16 years for the purposes of giving or withholding consent independent of any adult guardian. The regulations specify a hierarchy for determining who should be approached to give informed consent on behalf of a minor for their inclusion into a clinical trial. Table 1.2 lays out the hierarchy of who should provide informed consent for a minor. Ideally this consent should be given by a parent or person with parental responsibility.

Table 1.2 Hierarchy of informed consent for a minor.[68]

	Person who may give consent	Definition	Commentary
1	Parent	A parent or person with parental responsibility.	Should always be approached if available.
2	Personal legal representative	A person not connected with the conduct of the trial who is: (a) Suitable to act as the legal representative by virtue of their relationship with the minor, and (b) Available and willing to do so.	May be approached if no person with parental responsibility can be contacted prior to the proposed inclusion of the minor, by reason of the emergency nature of the treatment provided as part of the trial.

3	Professional legal representative	A person not connected with the conduct of the trial who is: (c) The doctor primarily responsible for the medical treatment of the minor, or (d) A person nominated by the relevant health care provider (e.g. An acute NHS Trust or Health Board)	May be approached if no person suitable to act as a personal legal representative is available. Informed consent must be given before the minor is entered into the trial.

Since 2004 there has been further legislation introduced, including the Blood Safety and Quality (Amendment) Regulations 2008. On occasion, the treatment given to a minor as part of a trial may need to be provided urgently, if this is the case there may not be time to obtain written consent of either the person with parental responsibility or a legal representative. As a result of this amendment minors can be entered into the trial and provided with the treatment under investigation without having first obtained informed consent. There are however a number of caveats to this:

- With regard to the nature of the trial and the case's individual circumstances it would be necessary to take urgent action for the purpose of the trial, however
- It is not reasonably practical to obtain informed consent prior to enrolling the subject
- The action taken is in accordance with a procedure approved by the ethics committee.

If a minor is recruited into a trial in an emergency situation without prior informed consent then informed consent must be obtained as soon as is reasonably possible. If this consent is withheld, then the subject must be withdrawn from the trial.[68]

In Scotland, the Clinical Trials Regulations also apply with a minor being defined as someone under the age of 16 years. However Scottish statute makes legal provision for young people, where they are considered competent, to consent to medical procedures or treatment. Those aged 16 and above are presumed to be competent until proven otherwise, they have the legal capacity to enter into any transaction, including, "....the giving by a person of any consent having legal effect."[71] Young people under 16 years can give legally binding consent if the medical practitioner believes them to be competent. "....a person under the age of 16 years shall have legal capacity to consent on his own behalf to any surgical, medical or dental procedure or treatment where in the opinion of a qualified medical

practitioner attending him, he is capable of understanding the nature and possible consequences of the procedure or treatment."[71] Thus in Scotland a young person's capacity allows them to refuse as well as consent to treatment. It is not entirely clear whether this Scottish statute also applies to research, however in the absence of specific guidance, the principles of the law relating to consent for procedures may reasonably be applied. However it must be remembered that the threshold for understanding relates to the complexity of the research being performed.[72]

Gillick Competency

Throughout the UK as a whole, minors, aged less than sixteen years can give consent if they are mature enough to have full understanding of what they are consenting to. A child with such understanding is referred to as being "Gillick Competent". This concept arose as a result of a House of Lords ruling in 1985 based on the case *Gillick v West Norfolk and Wisbech Area Health Authority (1985)*. In 1982 Victoria Gillick took the health authority and the Department of Health and Social Security to court in an attempt to prevent doctors giving contraception advice or treatment to under sixteen year olds without the consent of their parents. It was dismissed in the High Court, by Mr Justice Woolf.[73] It then went to the Court of Appeal where this decision was reversed, finding in favour of Mrs Gillick. In 1985 it then went to the House of Lords and the Law Lords ruled in favour of the original judgement of Mr Justice Woolf.[74]

> *"....whether or not a child is capable of giving the necessary consent will depend on the child's maturity and understanding and the nature of the consent required. The child must be capable of making a reasonable assessment of the advantages and*

disadvantages of the treatment proposed, so the consent, if given, can be properly and fairly described as true consent."[74]

Gillick competency is assessed using Lord Scarman's comments in his judgement of the case in the House of Lords. His comments are often referred to as the test of "Gillick competency"[75]:

"....it is not enough that she should understand the nature of the advice which is being given: she must also have a sufficient maturity to understand what is involved."

He also commented more generally on the rights of parents versus the rights of their children:

"Parental right yields to the child's right to make his own decisions when he reaches a sufficient understanding and intelligence to be capable of making up his own mind on the matter requiring decision."

Hitherto it has become common practice to describe an assessment of competency in terms of "Gillick competence" or the "Fraser guidelines" as though these were interchangeable. Contrary to this belief, despite arising out of the same case, the "Fraser guidelines" specifically addressed the issue of providing contraceptive advice or treatment without the knowledge of the patient's parent, whereas "Gillick competency" refers to the set of circumstances which demonstrate that a particular child has capacity to give informed consent in a particular situation.[74] Gillick competency is the primary doctrine with which competency in children is judged , whereas the Fraser guidelines are an adjunct to fuse Gillick competency with specific guidelines for children receiving contraceptive advice.[76]

If a child refuses to consent and the parent believes they should have treatment a healthcare professional can over-ride the child's lack of consent, thus in an orthodontic setting it would be possible for a clinician to provide orthodontic treatment to a minor even if it were against

the minor's wishes. If a child wants treatment or an intervention, for example contraception, but the parent does not, then this treatment can be provided, assuming that the child has sufficient maturity to understand what is involved and asks for the treatment. The healthcare professional is unable to share details of the child's treatment with the parent unless the child allows it.[77]

The Declaration of Helsinki guidance specifies that parental consent is required for all treatment in individuals under eighteen year of age, unless there is a clear reason why parental consent should not be given. However, in the United Kingdom, the Family Law Reform Act 1969 provides for 16 and 17 year olds to consent to treatment independently. The Royal College of Paediatrics and Child Health states that Gillick Competency is acceptable when consenting for enrolment in clinical research.[78] However, the question is raised as to whether children can consent to non-therapeutic research which is of no benefit to them. The generally held opinion is that there are often large benefits to be gained from heavily controlled child research. When the risk is minimal, parents can consent as long as the procedure is not against the child's best interests.[72]

Research Governance in the United Kingdom

In the United Kingdom, research is monitored primarily by guidance rather than legislation. However, there have been various incidences over the past decade to undermine confidence in this method of regulation. A prime example occurred in 2006, when six healthy volunteers, in a Phase I clinical trial at Northwich Park Hospital, had to be managed in Critical Care as at least four of the volunteers had suffered multiple organ failure.[79] An independent review of the trial found the regulation system to be at fault, that,

"the pre-clinical development studies that were performed with TNG1412 did not predict a safe dose for use in humans, even though current regulatory requirements were met".[79]

This incident was but one in a series of scandals undermining public and professional confidence in research regulation. In 2000 allegations were made that research was carried out on new-born infants in a North Staffordshire hospital without parental consent, although little evidence emerged in support of these opinions.[80] In 2001 a 24-year-old volunteer died in a clinical trial in Washington,[81] while in Bristol and Liverpool there have been scandals regarding the retention of children's body parts post-mortem without parental knowledge or consent.[82]

Legal aspects in the United Kingdom

In UK law (England and Wales) there is considerable guidance however, there is limited legislation governing the ethical aspects of clinical research. From a legal point of view, there are four main issues covering research and the ethics of research:

1. Is there a need for further statutory regulation of clinical research?
2. Is there true informed consent in clinical research?
3. Conflicts between confidentiality and research.
4. What degree and avenue of legal redress is appropriate in the case of injury acquired during the research?

In the United Kingdom, responsibility for clinical research in the NHS is shared by NHS research ethics committees (RECs) and local NHS Research and Development management.[83]

Ethical Approval and the Law

In the UK, if a research team fails to apply for ethical approval they are not breaking the law, unlike in USA.[84] This leaves an area of uncertainty as to whether the possibility of disciplinary action by an employing NHS Trust is enough to regulate this area sufficiently. The same is true of research carried out outside the NHS, as the GMC and other professional bodies potentially consider that carrying out research without appropriate ethical approval is ground for "serious professional misconduct". Royal College of Physicians' Guidelines state that,

> *"All medical research involving human subjects should undergo ethical review before it commences, in accordance with the principles that investigators should not be the sole judge of whether their research raises significant ethical issues".*[85]

Research Ethics Committees have a "Duty of Care" and therefore, direct legal responsibilities towards those taking part in research.

UK research guidance is supplemented by European Union law, including the European Clinical Trials Directive which has been law as of 2004.

Research Governance in the European Union

EU law takes precedent over any laws introduced by member states. For matters under the jurisdiction of the Treaty of Rome and subsequent treaties, most notably the Treaty of Amsterdam, the EU has the power to make laws affecting all member states. This is done either via regulations or directives. Regulations immediately become law in each member state, whereas directives oblige each government to enact the directive in local law, which in the UK manifests itself as an Act of Parliament. There are two main European Directives affecting ethics in research, namely the European Union Clinical Trials Directive 2001/20/EC (EUCTD)[48] and Good Clinical Practice Directive 2005/28 (GCP).[86] The EUCTD was enshrined into EU law in 2001 and became law in the UK with the Medicines for Human Use (Clinical Trials) Regulations 2004.[47] The aims of the EUCTD were to improve both the safety and efficacy of EU clinical trials. It strives to achieve these aims by:

1. Providing greater protection to subjects participating in clinical trials.
2. Increasing the number of patients entered into clinical trials.
3. Improving the efficiency of trial implementation.
4. Ensuring quality of conduct.
5. Harmonising regulation and conduct of clinical trials throughout Europe.
6. Ensuring best practice in ethical review and regulatory procedures.

Other aims were to improve the competitiveness of European research and apply to both commercial and investigator research.

Despite the EUCDT's laudable aims, even prior to its introduction, the academic community was expressing its concerns about the EUCDT, such as the potential adverse effects on translational research in particular,[87] upon which a negative impact has been demonstrated.[88]

A key aim in the EUCDT was to introduce harmonisation in the application for research ethics across the EU. Unfortunately, this did not materialise, resulting in excessively complex organisation required for multicentre trials involving different European countries.[89] Thus, trials are taking longer to set up and becoming more expensive to run,[90] highlighting a huge "Achilles' Heel" in EU research. Based on figures prior to the EU enlargement in 2004, the level of funding for non-commercial research was five times higher per head of capita in the USA than the EU.[91] Forecasts and surveys have indicated a 30-50% drop in the number of new non-commercial clinical trials started in the EU between 2004-2005.[92] This creates worrying concerns about the future of Europe's non-commercial research.

Publication Bias

Studies showing positive findings are more likely to be published.[93] Studies showing positive findings are also important for drug approval by the FDA. For a drug to be approved by the FDA Drug companies are obliged to provide two trials showing a statistical difference between the drug and a placebo, though it is not necessary to show a clinical difference between treatments. Kirsch *et al*[94, 95] performed a meta-analysis of clinical trials of anti-depressants comparing antidepressants with placebos.[95] This meta-analysis demonstrated a placebo response of 75% of the active drug response. The correlation between the placebo and active drug was 0.9. These findings were supported by similar results from the USA's Agency for Healthcare Policy and Research which found approximately a 20% drug-placebo difference in response rates i.e. 30-50% in an intention to treat meta-analysis of published antidepressant RCTs .[96] Drug companies are required to submit all trials involving a particular drug to the FDA as part of their NDA (New Drug Application) but this research is not required to be published as it is considered proprietary, though it is subject to the Freedom of Information Act. This study was then followed up in 2010[94] when a Freedom of

Information request acquired the information sent by various drug companies to the FDA as part of the drug approval process. The difference demonstrated here between drug and placebo was smaller than in the published data. Again, similar findings were reported elsewhere.[97]

Various registers have been introduced to make it more difficult not to publish negative trials and ensure that the published paper reports on what the trial was designed to test rather than "data dredging" to find something positive to publish. This is important because, based on the normal p value of 0.05, one out of every twenty measurements will be positive by chance. One such clinical trial registry is www.ClinicalTrials.gov, run by the USA's National Library of Health (NLM) at the National Institutes of Health. It was established in 1999 and is the world's largest trials registry holding registrations from over 93,000 trials from over 170 countries. The aim of the registry was not only to make it more difficult to manipulate or selectively publish data but also to allow patients to find out about experimental treatments and possibly enrol in these trials. In 2007, its range was expanded by the FDA requiring the sponsors of all drug, device and biological trials to register their studies on initiation (with the exception of Phase 1 Trials). In 2005, the International Committee of Medical Journal Editors began the requirement that a trial be registered before it began recruiting patients thus creating a record of planned outcomes prior to the commencement of the study. This requirement was necessary for a subsequent paper to be considered for publication. A recent report looking at outcomes of trials registered on www.ClinicalTrials.gov found industry sponsored trials reported positive findings 85% of the time compared to 50% for government funded trials and 72% funded by non-profit or non-federal organisations. Amongst these non-profit/non-federal trials, those with drug industry connections were more likely to report positive outcomes than those without (85% versus 61%).[98] In addition to statistically

significant differences between positive and negative findings, there was also a significant difference with regards to when the research was published. Drug company sponsored trials were least likely to be published within two years of study completion at 32%, whereas 54% of government trials and 56% of purely non-profit/non-federal trials were published within two years.[98] There is also the publication bias of studies not being published, this was as demonstrated to great effect in a meta-analysis by MacLean *et al*, examining the relative risk of dyspepsia from NSAIDs. Amongst the 37 trials described in the FDA review, only one was published in a peer reviewed journal.[99] However in this case no meaningful difference was found between the published and unpublished studies. Yet there were large differences in appropriate methods of randomisation and blinding between the published and unpublished studies. This may perhaps be a reflection of the different requirements for submission to peer reviewed journals and the FDA. Thus, unlike the work by Thase and Kirsch discussed previously, there were minimal differences between the published and unpublished clinical trials. MacLean also draws attention to the fact that all 37 trials examined in this analysis were sponsored by the pharmaceutical industry and thus the quality of their methodology could not be compared to non-pharmaceutical sponsored trials.[99]

Which Journals were investigated

The American Journal of Orthodontics and Dentofacial Orthopedics, Angle Orthodontist, European Journal of Orthodontics and Journal of Orthodontics (Formerly British Journal of Orthodontics) were identified as key journals to search because Sun *et al* identified that of the large amounts of clinically relevant material available to orthodontists, 45% of the articles were published in five orthodontic journals.[100] These were American Journal of Orthodontics and Dentofacial Orthopedics (formerly American Journal of Orthodontics), The Angle

Orthodontist, European Journal of Orthodontics, Journal of Orthodontics (formerly British Journal of Orthodontics) and International Journal of Adult Orthodontics and Orthognathic Surgery (ceased publication 2002). The International Journal of Adult Orthodontics and Orthognathic Surgery ceased publication in 2002, so it was excluded from this investigation. The four remaining journals were also chosen because 71.45% of orthodontic RCTs published between 2003 and 2007 were in these journals.[101]

The American Journal of Orthodontics and Dentofacial Orthopedics (formerly American Journal of Orthodontics) is one of the oldest orthodontic journals having been first published in 1915. It is the journal of the American Association of Orthodontists, its constituent societies, the American Board of Orthodontics and the College of Diplomates of the American Board of Orthodontics. It aims to publish original peer-reviewed articles focusing on all phases of clinical orthodontic treatment. In 2010 it was the highest ranked orthodontic journal in terms of citations and impact factor. It is not surprising that it is the highest in terms of citations as it publishes many more articles than the other journals, as can be seen in Table 5.1.[102]

The Angle Orthodontist is the journal of the Edward H. Angle Society of Orthodontists. It is the only major orthodontic journal with a non-commercial, non-profit publisher -- The E. H. Angle Education and Research Foundation. The journal states that it values this freedom from commercial interests which allows it to operate exclusively in the best interests of our readers and authors. It is completely free to access.[104]

The European Journal of Orthodontics states it "publishes scientific papers aimed at all orthodontists", thus implying a focus on scientific as well as clinical research. It publishes research papers which "extend the scientific basis of orthodontics". The journal was first published in 1979, despite being the journal of the European Orthodontic Society it is happy

to publish articles from around the world but aims to provide a forum for orthodontists in Europe.[107]

The Journal of Orthodontics (formerly the British Journal of Orthodontics) is the Journal of the British Orthodontic Society, despite this it has an international circulation and publishes articles from all over the world. It provides the most guidance on the scope and type of articles it aims to publish, namely "high quality, evidence-based, clinically orientated or clinically relevant original research papers that will underpin evidence based orthodontic care. It particularly welcomes reports on prospective research into different treatment methods and techniques but also systematic reviews, meta-analyses and studies which will stimulate interest in new developments."[108]

Journal Requirements for Publication

Levels of evidence of ethical research required prior to publication.

American Journal of Orthodontics and Dentofacial Orthopedics

The AJODO refers authors to the "Uniform Requirements for Manuscripts submitted to Biomedical Journals".[16] A conflict of interest statement must be provided with each submitted article. RCTs should be written up as per CONSORT Guidelines. However in its guidance to authors it states that Institutional Review Board approval must be obtained but makes no mention of informed consent. It advises that guest editorials, letters and review articles may be rejected if a conflict of interest exists.[102]

The AJODO also makes use of the PERK (Publishing Ethics Resource Kit) resource,[103] as us ed by all of Elsevier's journals. This is an online resource to support journal editors in

handling ethical issues in publishing, dealing with such matters as unethical behaviour by reviewers and misreporting of statistics.

The AJODO is also a member of the Committee on Publication Ethics (COPE).[19] COPE is a registered charity, concerned with the integrity of peer reviewed journals and includes many major publishing houses including Elsevier (AJODO) and Oxford University Press (EJO). It provides a forum for academic editors to discuss issues related to the ethical integrity of work submitted to or published in their journals. It also encourages members to seek investigation into possible episodes of research misconduct by applicants.

Angle Orthodontist

The guidelines for authors states that "if humans or animals were involved in the work" it requires "a statement that the rights of the human or animal subjects were protected and that approval was obtained from an identified institutional review board or its equivalent."[104] On contacting the editor he clarified the AO's editorial position by stating that the AO "reject manuscripts that demonstrate flagrant ethical abuse such as treatments that are not appropriate for the patient and any other procedure that is not in the patient's best interest". and "require authors to commit to any financial interests they may have with regard to their research."[105]

European Journal of Orthodontics

The EJO is a member of COPE. It draws authors' attention to the Declaration of Helsinki, CONSORT statement on randomized controlled trials and the Guiding Principles in the Care

and Use of Laboratory Animals.[106] This journal, like the JO, reserves the right not to accept papers unless adherence to the principles embodied in these documents is apparent. Ethical approval, where applicable, must have been obtained and details of such must be contained within the manuscript.[107]

Journal of Orthodontics

The guidance to authors of the JO states that all papers being submitted for consideration should contain a statement to the effect that the research has ethics committee approval and conforms to the Declaration of Helsinki. A statement to this effect should be included in the submitted paper.[108] The Editor reserves the right to request a copy of this letter from the relevant ethics committee or indeed a letter from the relevant ethics committee confirming that ethical approval was not required. The guidance also draws the authors' attention to the Guide for the Care and Use of Laboratory Animals.[106]

Classification of Articles

Articles were classified as RCTs, CCTs or not eligible using the Cochrane Collaboration Glossary.[109]

Clinical Trial

"An experiment to compare the effects of two or more healthcare intervention. Clinical trial is an umbrella term for a variety of designs of healthcare trials, including uncontrolled trials, controlled trials and randomised controlled trials (also called Intervention Study). "[109]

Randomised controlled trial (RCT)

"An experiment in which two or more interventions, possibly including a control intervention or no intervention, are compared by being randomly allocated to participants. In

most trials one intervention is assigned to each individual but sometimes assignment is to defined groups of individuals (for example in a household) or interventions are assigned within individuals (for example, in different orders or to different parts of the body)."[109]

Controlled Clinical Trial (CCT)

"Indexing term used in MEDLINE and CENTRAL. Within CENTRAL it refers to trials using quasi-randomisation, or trials where double blinding was used but randomisation was not mentioned."[109]

Chapter 3: Calibration and Reliability Studies

Calibration Study

Null Hypothesis

There is no difference between RF's identification of RCTs and CCTs and that of the Cochrane Oral Health Group Handsearching Test[110] against the alternative hypothesis of a difference.

Aim

To calibrate RF in the detection of Randomised Controlled Trials (RCTs) and Controlled Clinical Trials (CCTs) as defined by the Cochrane Collaboration.

Sample Frame

Cochrane Collaboration Oral Health Group's list of articles to assess as part of its handsearching test.

Method

The Cochrane Collaboration Oral Health Group handsearching test was undertaken in January 2010 prior to commencement of the handsearching for this study.

Results

RF passed the handsearching test.

Reliability Study

Null Hypothesis

There was no difference in the selection of papers fulfilling the criteria to be classified as either RCTs or CCTs by RF over time against an alternative hypothesis of a difference.

Aim

To determine the intra-examiner reliability of RF over time.

Sample Frame

Articles published in the American Journal of Orthodontics and Dentofacial Orthopedics (AJODO), Angle Orthodontist (AO), European Journal of Orthodontics (EJO) and Journal of Orthodontics (JO), (Formerly British Journal of Orthodontics) between 1st January 2008 and 31st December 2008.

Method

All issues of the AJODO, AO, EJO and JO published between 1st January 2008 and 31st December 2008 were handsearched to identify all articles reporting Randomised Controlled Trials (RCTs) and Controlled Clinical Trials (CCTs). This was performed in January 2010. These journals were recategorised again, after three months in April 2010, so as to allow the initial details to be forgotten. To prevent examiner fatigue only two journals were examined at any one time. The results were analysed for reliability.

Intra-examiner agreement was assessed by tabulating the number of agreements and disagreements for each item, i.e. RCT or not and subsequently calculating a kappa score.

Inclusion Criteria

Articles that fulfilled the Cochrane Collaboration Oral Health Group handsearching criteria for RCTs and CCTs were included in the study. These articles had to meet the following criteria:

1. "The study compares ***healthcare*** treatment/interventions in ***human beings,***
2. The study is ***prospective*** in nature, i.e., the treatments/interventions are planned prior to the experiment taking place, and exposure to each intervention is under the control of the study investigators,
3. ***Two*** **or more** treatments/interventions are compared to one another (or one may be a no treatment control group),
4. The most important aspect is that assignment to a particular treatment/intervention is intended to be ***random,*** i.e., not deliberately selected in any way. Units of randomisation may be individuals, groups (communities, schools, or hospitals), organs or other parts of the body (such as teeth). If the method of selection is quasi-random or not stated, then we may give the study the benefit of the doubt and include it as a Controlled Clinical Trial (CCT)".[110]

Exclusion Criteria

All articles which do not fulfil the above criteria.

Statistical Methods

Percentage agreement and Kappa statistic were used to determine reliability.

Results

The kappa score was 0.98 indicating excellent intra-examiner reliability.

Chapter 4: Main Study

Aims

This study aimed to:

- Assess the number of Randomised Controlled Trials (RCTs) and Controlled Clinical Trials (CCTs) published in the American Journal of Orthodontics and Dentofacial Orthopedics (AJODO), Angle Orthodontist (AO), European Journal of Orthodontics (EJO) and Journal of Orthodontics (JO) (formerly British Journal of Orthodontics) between 2001 and 2010.

- Determine the number of these trial reports which recorded having obtained ethical approval and informed consent.

- Determine whether the omission of a statement referring to obtaining ethical approval and informed consent was an oversight of the authors or an omission of the trial process.

- Determine the number of authors, number of centres, location, involvement of a statistician and the inclusion of random* in either the title or abstract or body of the RCTs.

- Determine whether the factors above influence an RCT's likelihood of having recorded that ethical approval and informed consent had been obtained.

- Determine the sensitivity of identifying RCTs in the four journals under consideration using various electronic search methods, namely MEDLINE search via PubMed and Ovid for publication type RCT and PubMed free text search for random* AND orthodontic.

- Compare the electronic search methods with handsearching as the gold standard.

Null Hypotheses

1. Orthodontic randomised controlled trials and controlled clinical trials:

    i. Do not have ethical approval from an institutional review board or equivalent.

    ii. Do not demonstrate that informed consent had been obtained from participants.

2. The number of authors, number of centres, location, involvement of a statistician, year of publication and the inclusion of random* in either the title or abstract or body of the article were not predictive of an RCT having obtained ethical approval and informed consent.

3. All orthodontic RCTs, published in the four journals, had random* in the title, abstract and body of the article.

4. There was no difference between the sensitivity of electronic searching versus that of handsearching to identify orthodontic RCTs against an alternative hypothesis of a difference.

Design

A retrospective observational study.

Sample Size

Previous work identified that only 11% of papers reporting RCTs and CCTs in three major orthodontic journals published between 1989-98 demonstrated that both informed consent and ethical approval had been obtained.[4] It is now a prerequisite for the publishing of an RCT or CCT that these criteria are included in the article, so one would expect the frequency of concordance with these criteria to be 100%. To identify such a large change in compliance

would require a sample size of 2-4 papers per group. Instead, the change in reporting rates over time was used to calculate the sample size. Harrison[4] reported approximately a doubling of reporting incidence from 1989-93 to 1994-98. A study reporting similar issues in oral and maxillofacial surgery also found approximately a doubling of papers with documented evidence of both ethical approval and informed consent having been obtained between 2005-07. [111] Therefore a change in incidence of clinical trials having obtained both ethical approval and informed consent from 11% to 22% was investigated. This was used in Pocock's formula (Fig 5.1)[112] giving a total of 177 clinical trials. However when all of the journals were searched a total of 89 CCTs and 218 RCTs were found. It was decided to include all of these trials in the analysis.

Fig 5.1. Pocock's Formula

$$\text{Number per group} = \frac{[p_1(1-p_1) + p_2(1-p_2)]}{(p_2-p_1)^2} \times f(ab)$$

p_1 = proportion of RCTs in original research with ethical approval and informed consent

p_2 = proportion of expected RCTs in current research with ethical approval and informed consent

f(ab) = factor (type I error (0.05), type II error (0.2))

$$\text{Number per group} = \frac{[0.11(1-0.11) + 0.22(1-0.22)]}{(0.22-0.11)^2} \times 7.9$$

$$= \frac{[(0.11 \times 0.89) + (0.22 \times 0.78)]}{(0.11)^2} \times 7.9$$

= 22.46 x 7.9

= 177.42 per group

=354.84

Method

Sample Frame

Articles were identified in:

- **A**merican Journal of Orthodontics and Dentofacial Orthopedics (formerly American Journal of Orthodontics) (**A**)
- The A**n**gle Orthodontist (**N**)
- **E**uropean Journal of Orthodontics (**E**)
- **J**ournal of Orthodontics (formerly British Journal of Orthodontics) (**J**)

These journals were chosen as Sun *et al* identified that 45% of orthodontic articles were published in five orthodontic journals,[100] four being journals listed above and the fifth being the International Journal of Adult Orthodontics and Orthognathic Surgery which ceased publication in 2002 which was therefore excluded. These four journals were also chosen because 71.45% of orthodontic RCTs published between 2003 and 2007 were published in these journals.[101] In estimating the number of papers published in each journal, original research papers and case reports were included, whilst editorials, letters to the editor, erratum and commercial promotions were excluded.

Identification of clinical trials

All editions of the AJODO, AO, EJO and JO, published between January 2001 and December 2010, were handsearched to identify all papers reporting RCTs and CCTs.

Inclusion Criteria

Articles fulfiling the Cochrane Collaboration Oral Health Group Handsearching definitions for either RCTs or CCTs.[110]

Exclusion Criteria

All articles which did not fulfil the above criteria.

Included Articles

Once identified, each article was assigned a reference code comprising of:

- Journal single letter identifier e.g. (**A**, **N**, **E**, **J**),
- Year of Publication,
- Month of Publication
- Sequential Number of that article from the journal's content page,
- For Example, N/2010/Jan/6 = Angle Orthodontist, 2010, January, Article 6.

The total number of articles was calculated for both RCTs and CCTs. A separate list was kept for both RCTs and CCTs.

Assessment Criteria and Outcomes

Each article, reporting an RCT or CCT was assessed for the following items:

1. What type of trial was reported in the article, RCT or CCT.
2. Inclusion of a statement that:
    i. Ethical approval had been obtained from a relevant ethics committee.

ii. Informed consent had been obtained from and freely given by participants.

These outcomes were assessed as present or absent.

Clarification of absent status for RCTs

- In the RCTs, if both ethical approval and informed consent were absent, the first author was contacted directly for clarification of the paper's status with respect to the above criteria.

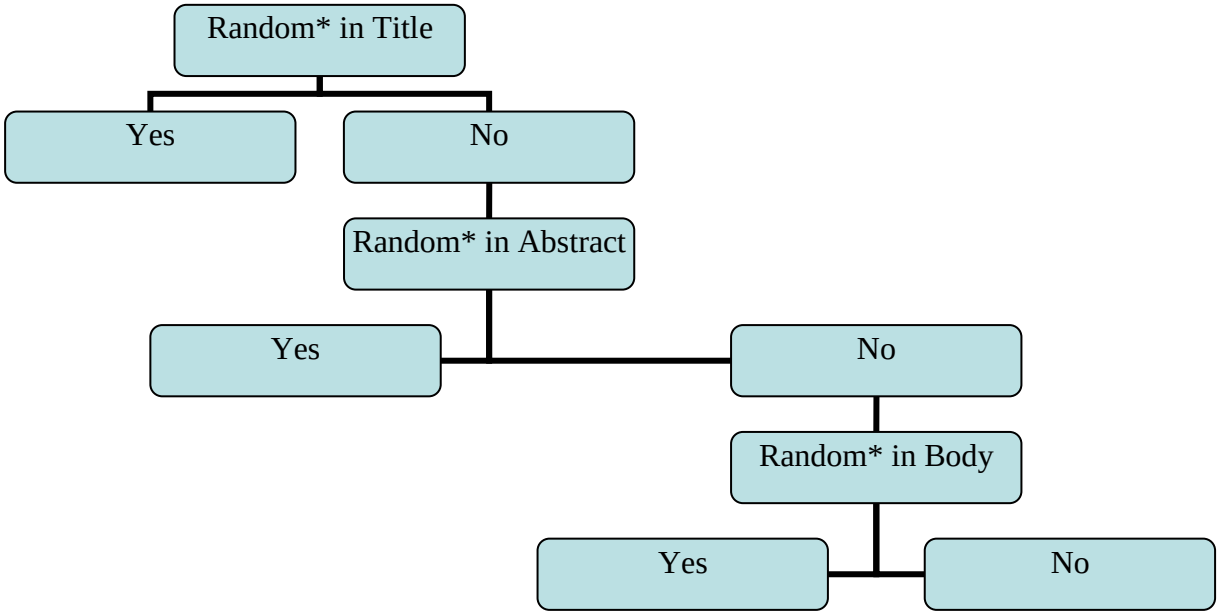
- If there was no response when attempts were made to contact the author or they were uncontactable then these papers were listed as not having obtained ethical approval or informed consent as these criteria were not mentioned in the article.

The RCTs were further assessed as follows:

1. The journal the article was published in: namely the AJODO, AO, EJO or JO.
2. The number of authors: 1-3, 4-6 or >6.
3. How many centres the RCT was performed in: 1, 2, $\geq$3.
4. The location of origin of the RCT: EU (excluding the UK), UK, USA or Other.
5. The involvement of a statistician: yes or no.
6. The year of publication: between 2001 and 2005 inclusive or 2006 and 2010 inclusive.
7. Random* in the title: yes or no.
8. Random* in the abstract, if not in the title: yes or no.

9. Random* in the body of the article, if not in the title or abstract: yes or no. (See Figure 5.2.)

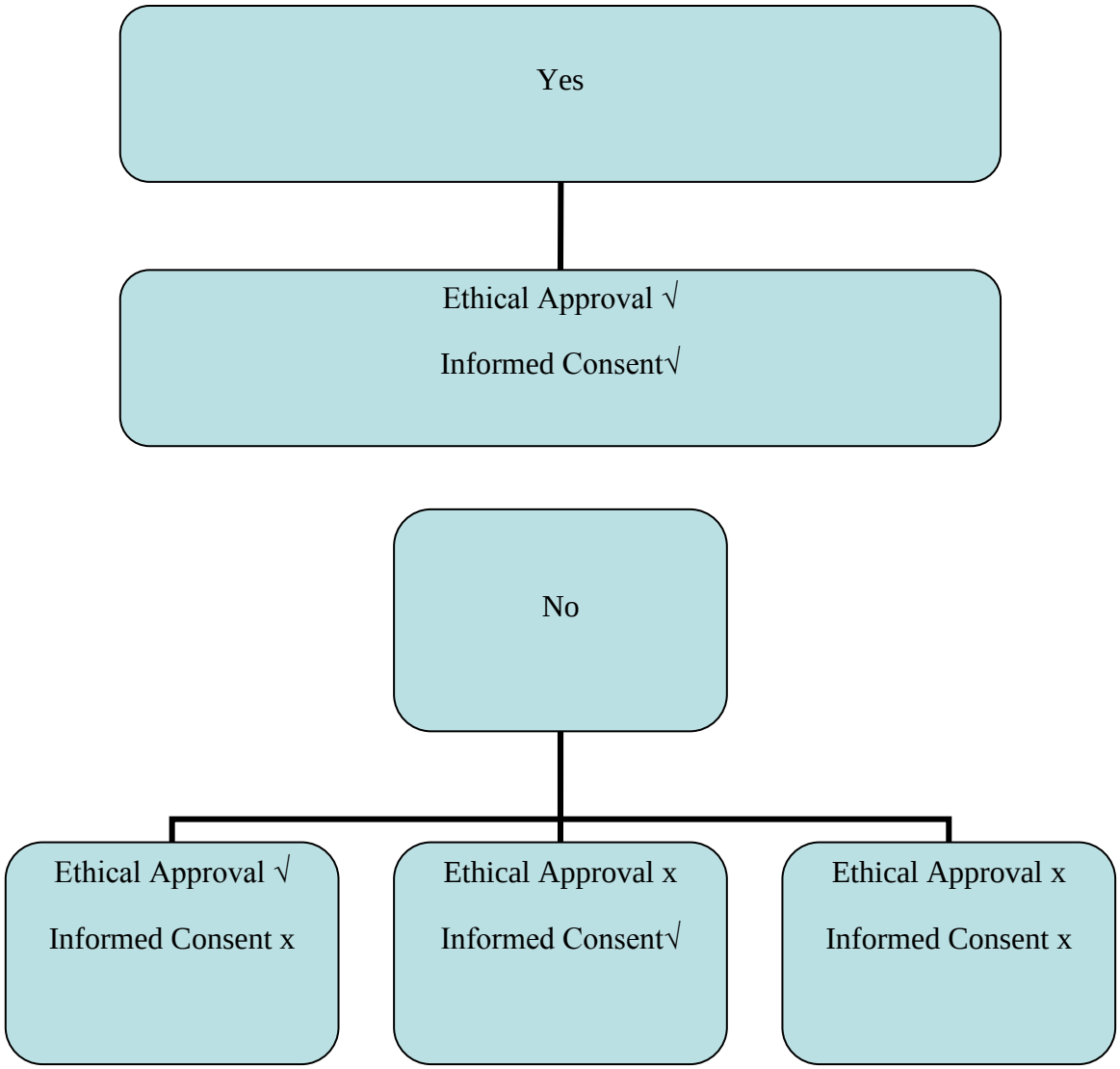
Figure 5.2. Location of Random* in paper.



Factors influencing data collection and analysis for the RCTs

The impact of various factors on the likelihood of the RCT having obtained both ethical approval and informed consent or not was evaluated. The RCTs were divided into two groups, those which had both ethical approval and informed consent and those which did not. The "not" group had either ethical approval or informed consent or neither. This subdivision was performed on the advice of the statistician because more subdivisions would not have provided meaningful data as the numbers were too small, see Figure 5.3. It is recognised that this categorisation is descriptively important, as it implies that having either ethical approval or informed consent is to be regarded in the same light as obtainment of neither.

Fig 5.3. Subdivision of RCTs with ethical approval and informed consent or not.



The authors of the RCTs which had neither ethical approval or informed consent were contacted as it was felt that the results could be potentially biased if the authors had actually obtained both ethics and consent but had inadvertently left out this fact. Therefore they would been recorded as not having obtained either but would it actual fact have obtained both. By contacting the authors it was hoped that the exact position of their article with regards to ethical approval and informed consent would be clarified, for example, whether they had definitely not obtained ethical approval and informed consent or whether they had omitted a

statement stating compliance with these criteria simply by accident. The authors were contacted via email using the email address provided on the article, each email was sent twice. A sample of an email and response can be seen in Appendix 2. However, despite these numerous attempts to contact authors, the response rate was extremely low with only two authors responding, a 3.4% response rate, therefore this was considered to be insignificant.

Data Entry

The data were entered into two customised Microsoft Excel spreadsheets (Microsoft Office 2003, Microsoft Corporation, Redmond, WA98052-7329, USA). One customised for the CCT checklist and the other for the RCT checklist. The CCT checklist spreadsheet was made up of three columns for each criterion and a row for each CCT assessed. The spreadsheet for the RCT checklist comprised of sixteen columns representing the criteria being assessed and each row representing the RCT to be assessed. A maximum of three journals and the articles contained within were scored at any one time in order to prevent examiner fatigue and hence decrease scoring errors.

Reliability

To ensure that an acceptable level of intra-examiner reliability was being maintained for both assessment of the trials as RCTs or CCTs and the RCT and CCT checklists a reliability study was conducted during the main study.

A list of ten per cent of the journal volumes were prepared by JEH using a random number generator,[113] the articles in these journals were reclassified. The RCTs and CCTs were reassessed by RF six months after the completion of the data collection for the entire sample. RF was blinded to the initial results whilst re-examining the articles. The reliability was assessed using the Kappa statistic and percentage agreement.

Statistical Methods

Descriptive statistics were used to analyse baseline data. Chi-squared test (χ^2) was used to assess categorical data and risks ratio (RR) and 95% confidence intervals (95% CI) was used to assess binary data.

A multilinear regression was applied to the RCT data to assess which factors were the most important in predicting compliance with ethical approval and informed consent.

The sensitivity of various methods of electronic searching was assessed.

Statistical Analysis

This was undertaken by using SPSS, version 19.[114]

Chapter 5: Results

The results are subdivided into seven sections:

5.1.General Characteristics

5.2.RCTs

5.3.CCTs

5.4.Comparison of RCTs and CCTs

5.5.Factors influencing ethical approval and informed consent in RCTs

5.6.Identification of RCTs using various search methods.

5.7.Results of calibration and reliability studies.

5.1. General Characteristics

All issues of the AJODO, AO, EJO and JO, published over the ten year period, were assessed for RCTs and CCTs. A total of 4784 articles were identified in 287 issues of the journals examined between 1st January 2001 and 31st December 2010 as seen in Table 5.1. A small number of these were RCTs and CCTs, 4.6% and 1.9% respectively. There were significant differences between the journals in the proportion of RCTs (χ^2 55.5; degree of freedom (df) =3; p=0.001) and CCTs (χ^2 8.12; df=3; p=0.044) that were published. The AO published the smallest percentage of RCTs at 2.8% and the AJODO published 36 CCTs, which comprised 40.5% of all CCTs.

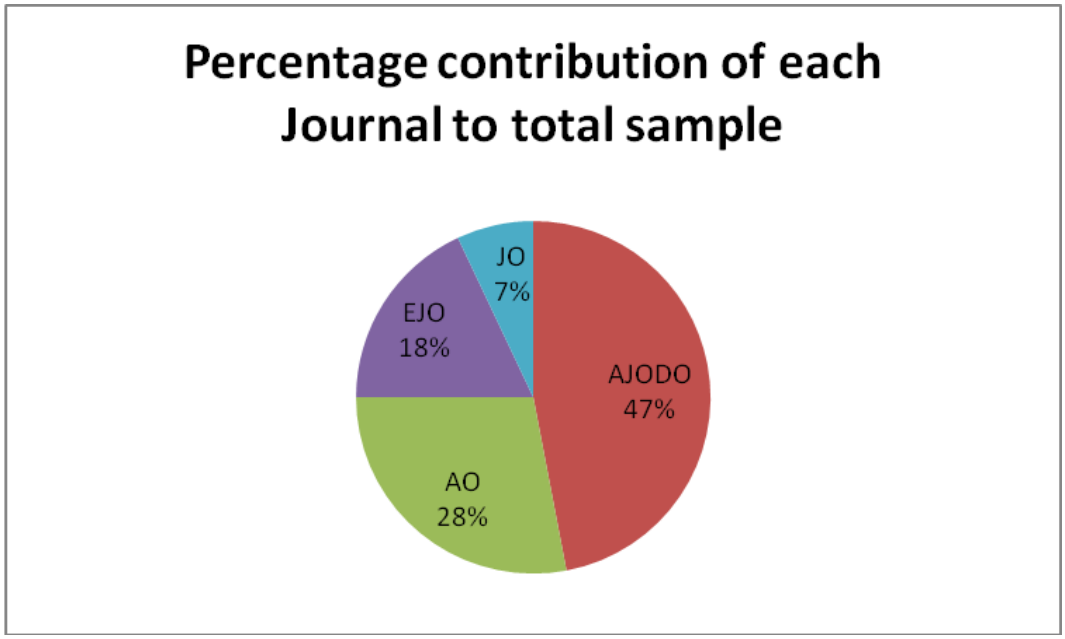
Table 5.1 Overall number of journal issues and articles published

Journal	Number of issues	Number of articles	Percentage of articles	Number of RCTs	Percentage of all RCTs	RCTs as a percentage of all articles published in the journal	Number of CCTs	Percentage of all CCTs	CCTs as a percentage of all articles published in the journal
AJODO	125	2242	46.9%	119	54.6%	5.3%	36	40.5%	1.6%
AO	60	1341	28%	38	17.4%	2.8%	33	37.1%	2.5%
EJO	61	879	18.4%	45	20.6%	5.1%	19	21.4%	2.2%
JO	41	322	6.7%	16	7.3%	5%	1	1.1%	0.3%
TOTAL	287	4784	100%	218	100%	4.6%	89	100%	1.9%

Number of journals and articles published

The AJODO published the majority of articles (2242/4784=46.9%), while the fewest articles were published in the JO (322/4784=6.7%). As well as publishing more articles per journal the AJODO also published more issues each year, from 2006 it published a supplementary April issue also, further increasing the number of articles published. In comparison the AO and EJO publish bimonthly and the JO quarterly. The significant contribution of the AJODO can be visualised in Figure 5.1.

Figure 5.1 Percentage contribution of each Journal to sample.



Number of RCTs and CCTs as a percentage of articles published

RCTs and CCTs comprised a small number of all articles published over the ten year time period. RCTs made up 4.6% of all articles and CCTs 1.9% respectively, as seen in Table 5.2.

Table 5.2 Number of RCTs and CCTs as a percentage of articles published.

Clinical Trial Type	Total	Percentage of total articles published (4784 articles)
RCT	218	4.56%
CCT	89	1.86%

5.2. RCTs

Number of RCTs per journal

A total of 218 RCTs were published in the four journals between 1st January 2001 and 31st December 2010, comprising 4.6% of all articles published in the four journals, as seen in Table 5.3. 54.6% of these were published in the AJODO, RCTs comprised 5.3% of the articles published in the AJODO. This was a similar percentage for the EJO and JO at 5.1% and 5% respectively. The AO's percentage of RCTs compared to the total number of articles was lower than the other journals at 2.8%. These differences were significant differences (χ^2 =55.5; df=3; p<0.001).

Table 5.3 RCT numbers and journal of publication.

Journal	Number of RCTs	Percentage of all RCTs	RCTs as a percentage of all articles published in the journal
AJODO	119	54.6%	5.3%
AO	38	17.4%	2.8%
EJO	45	20.6%	5.1%
JO	16	7.3%	5%
Overall	**218**	**100%**	**4.6%**

RCTs with ethical approval and informed consent

Of the 218 RCTs published 106 had both ethical approval and informed consent, 59 had neither, 32 had obtained ethical approval only and 21 informed consent only. Thus 49% of RCTs were properly reported with ethical approval and informed consent, as can be observed in Table 5.4; Appendix 4, Figure 1.

Table 5.4 Number of RCTs with ethical approval and informed consent

	Number of RCTs	Percentage
Ethical Approval and Informed Consent	106	48.6%
No Ethical Approval or Informed Consent	59	27.1%
Ethical Approval only	32	14.7%
Informed Consent only	21	9.6%
Overall	218	100%

5.3. CCTs

Number of CCTs per journal

Between 2001 and 2010, 89 CCTs were published in the four journals examined, comprising 1.9% of all articles published in the four journals.

36 were published in the AJODO and 33 in the AO. The JO published one CCT only during this time period, so CCTs comprised 0.3% of all JO articles published in the ten year interval. As a percentage of total articles published the AO and EJO publish the greatest percentage of CCTs at 2.5% and 2.2% respectively. These differences were significantly different (χ^2 =8.12; df=3; p=0.044). The distribution of these CCTs is seen in Table 5.5.

Table 5.5 CCT numbers and journal of publication.

Journal	Number of CCTs	Percentage of all CCTs	CCTs as a percentage of all articles published in the journal
AJODO	36	40.5%	1.6%
AO	33	37.1%	2.5%
EJO	19	21.3%	2.2%
JO	1	1.1%	0.3%
Overall	**89**	**100%**	**1.9%**

CCTs with ethical approval and informed consent

Of the 89 CCTs published, 32 had both ethical approval and informed consent, 36 had neither, 8 had obtained ethical approval only and 13 informed consent only. Thus, only 36% of CCTs were properly reported with ethical approval and informed consent, as can be observed in Table 5.6; Appendix 4, Figure 2.

Table 5.6. Number of CCTs with ethical approval and informed consent

	Number of CCTs	Percentage
Ethical Approval and Informed Consent	32	36%
No Ethical Approval or Informed Consent	36	40.4%
Ethical Approval only	8	9%
Informed Consent only	13	14.6%
Overall	89	100%

5.4. Comparison of CCTs and RCTs

RCTs were generally better reported with regards to ethical issues than CCTs. 48.6% of RCTs had reported obtaining both ethical approval and informed consent whereas only 36% of CCTs had obtained same, as can be seen in Table 5.7; Apprendix 5, Figure 3. The number of CCTs which had obtained neither ethical approval or informed consent was higher for the CCTs at 40.4%, compared to the RCTs at 27.1%. These differences were significantly different (χ^2 =8.9, df=3, p=0.031).

Table 5.7. Number of RCTs and CCTs with ethical approval and informed consent

	Number of RCTs	Percentage of RCTs	Number of CCTs	Percentage of CCTs
Ethical Approval and Informed Consent	106	48.6%	32	36%
No Ethical Approval or Informed Consent	59	27.1%	36	40.4%
Ethical Approval only	32	14.7%	8	9%
Informed Consent only	21	9.6%	13	14.6%
Overall	218	100%	89	100%

5.5. Factors influencing ethical approval and informed consent in RCTs

A variety of trial characteristics were examined to investigate if any predicted the RCT having obtained ethical approval and informed consent. The factors investigated were;

- Journal of Publication
- Number of Authors
- Number of Centres
- Location of Origin
- Involvement of a Statistician
- Year of Publication
- Random* in Title
- Random* in the Abstract, if not the Title
- Random* in the Article, If not the Title or Abstract.

Journal of Publication

The journal has a statistically significantly (p=0.004) impact on the probability of the RCTs published in differing journals having ethics and informed consent.

The overall average for papers having recorded both ethical approval and informed consent is 48.6%, this belies a large range between the different journals with 75% of RCTs published in the JO having obtained both ethical approval and 26.3% of those published in the AO having obtained same, this can be visualised in Table 5.8; Appendix 4, Figure 4.

Table 5.8. Journal of Publication and number of RCTs with ethical approval and informed consent.

Journal	Ethics and consent	Not ethics and consent
AJODO	58 (48.7%)	61 (51.3%)
AO	10 (26.3%)	28 (73.7%)
EJO	26 (57.8%)	19 (42.2%)
JO	12 (75.0%)	4 (25.0%)
Overall	106 (48.6%)	59 (51.4%)

Number of authors

The number of authors contributing to an RCT was very statistically significantly associated with the paper having obtained ethical approval and informed consent, $p<0.001$.

As seen in Table 5.9; Appendix 4, Figure 5, 94.7% of RCTs, with greater than six authors, had ethical approval and informed consent compared to 45.5% of those with one to three authors. These differences were significant ($\chi^2=17.8$; df=2; $p<0.001$).

Table 5.9. Number of Authors and number of RCTs with ethical approval and informed consent or not.

Number of authors	Ethics and Consent	Not Ethics and Consent
1-3	35 (45.5%)	42 (54.5%)
4-6	53 (43.4%)	69 (56.6%)
>6	18 (94.7%)	1 (5.3%)
Overall	106 (48.6%)	112 (51.4%)

Number of centres

The number of centres at which the trial was carried out was a significant factor in determining compliance with ethical approval and informed consent, with (χ^2 =9.62; df=2; p=0.008). Although the majority of the RCTs were performed at single centre sites, when they were performed in 2 or more sites they were much more likely to have obtained both ethical approval and informed consent, as can be seen in Table 5.10; Appendix 4, Figure 6. RCTs performed in one centre did not have ethical approval and informed consent in 56% of trials examined whereas those in three or more centres had ethical approval and informed consent in 71.4% of RCTs.

Table 5.10. Number of Centres and number of RCTs with ethical approval and informed consent or not.

Number of Centres	Ethics and consent	Not ethics and consent
1	80 (44%)	102 (56%)
2	16 (72.7%)	6 (27.3%)
≥3	10 (71.4%)	4 (28.6%)
Overall	106 (48.6%)	112 (51.4%)

Location of Origin

Location of origin was sub-divided into the following:

1. EU (Excluding UK)
2. UK
3. USA
4. Other

Any RCTs from more than one country were classified according to the first author.The exact number of RCTs published by each country can be seen in Table 5.11; Appendix 4, Figure 7.

All RCTs performed in the EU were carried out in countries which had obtained their EU membership status decades prior to the date of research publication. It may thus be assumed that all research was therefore carried out under the auspices of EU legislation and guidance. Research from the EU countries had obtained ethical approval and informed consent for 55% of RCTs and not for 45%.

Research from the UK was analysed separately. This decision was made due to the disproportionately large number of RCTs published by authors from the UK and it was felt this merited its own individual assessment. RCTs published by UK authors showed the highest level of compliance with obtaining both ethical approval and informed consent at 65.2%, which along with the EU authors was the highest level, see Table 5.12. However, there was a low level of both ethical approval and informed consent obtained by RCTs performed in the USA at 29.3%. These differences were statistically significant (χ^2 =15.7; df=3; p=0.001).

Table 5.11. Number of RCTs published by each country.

Country of Publication	Number of RCTs
1. EU excluding UK	
Austria	1
Belgium	1
Denmark	1
Finland	6
Germany	7
Greece	5
Italy	9
Netherlands	3
Sweden	7
2. UK	40
3. USA	41
4. Other	
Australia	10
Brazil	19
Canada	3
China	3
Egypt	1
India	3
Israel	3
Japan	2

New Zealand	**1**
Norway	**2**
Peru	**1**
Saudi	**1**
Switzerland	**1**
Thailand	**1**
Turkey	**20**

Table 5.12. Location of Origin and number of RCTs with ethical approval and informed consent or not.

Location of origin	Total number of RCTs Percentage of Total RCTs	Ethics and consent	Not ethics and consent
EU (Excluding UK)	40 (18.4%)	22 (55%)	18 (45%)
UK	66 (30.3%)	43 (65.2%)	23 (38.4%)
USA	41 (18.8%)	12 (29.3%)	29 (70.7%)
Other	71 (32.6%)	29 (40.8%)	42 (59.2%)
Overall	218 (100%)	106 (48.6%)	112 (51.4%)

Involvement of a statistician

The involvement of a statistician did not influence whether ethical approval and informed consent were reported, OR 1.13 (95% CI 0.63, 2.04).

The assessment of whether a statistician was involved in the RCT was based on whether a statistician was one of the authors or thanked in the acknowledgements section. When the exact position of the author was unclear, for example if it was stated only that they worked in the "Orthodontic Department" their name and university was searched online via Google to investigate if they were a statistician. For those RCTs which stated that a statistician had been involved, ethical approval and informed consent were obtained in 50.8% of RCTs, whereas if a statistician was not involved, ethical approval and informed consent were obtained in 47.8% of RCTs, as seen in Table 5.13; Appendix5, Figure 8.

Table 5.13. Involvement of a statistician and percentage of RCTs with ethical approval and informed consent or not.

Statistician	Ethics and consent	Not ethics and consent
Yes	31 (50.8%)	30 (49.2%)
No	75 (47.8%)	82 (52.2%)
Overall	106 (48.6%)	112 (51.4%)

Year of Publication

The time period 1st January 2001 to 31st December 2010 was divided into papers published between 2001 and 2005 inclusive or 2006 and 2010 inclusive. These dates were chosen due to the instigation of the European Clinical Trials Directive in 2004. Of those RCTs published in 2005 or earlier 63.3% did not have ethical approval and informed consent compared with 43% of RCTs published between 2006 and 2010. RCTs published in 2006 or later were significantly more likely to have ethical approval and informed consent, OR=2.29 (95% CI 1.32, 3.99) than those published between 2001 and 2005, as seen in Table 5.14; Appendix 4, Figure 9.

Table 5.14. Year of Publication and number of RCTs with ethical approval and informed consent or not.

Year of Publication	Ethics and consent	Not ethics and consent
2001-2005	33 (36.7%)	57 (63.3%)
2006-2010	73 (57.0%)	55 (43.0%)
Overall	106 (48.6%)	112 (51.4%)

Random in Title*

Of the 218 RCTs found, only 77, (35.5%) had random* in the title, see Figure 5.2. Of those RCTs with random* in the title, 66.2% had both ethical approval and informed consent, compared with 48.6% of RCTs that did not. If random* was in the title, this was significantly associated with the RCT having obtained both ethical approval and informed consent (OR=3.07, 95% CI 1.75, 5.48), see Table 5.15.

Figure 5.2. Percentage of RCTs with random* in the title.

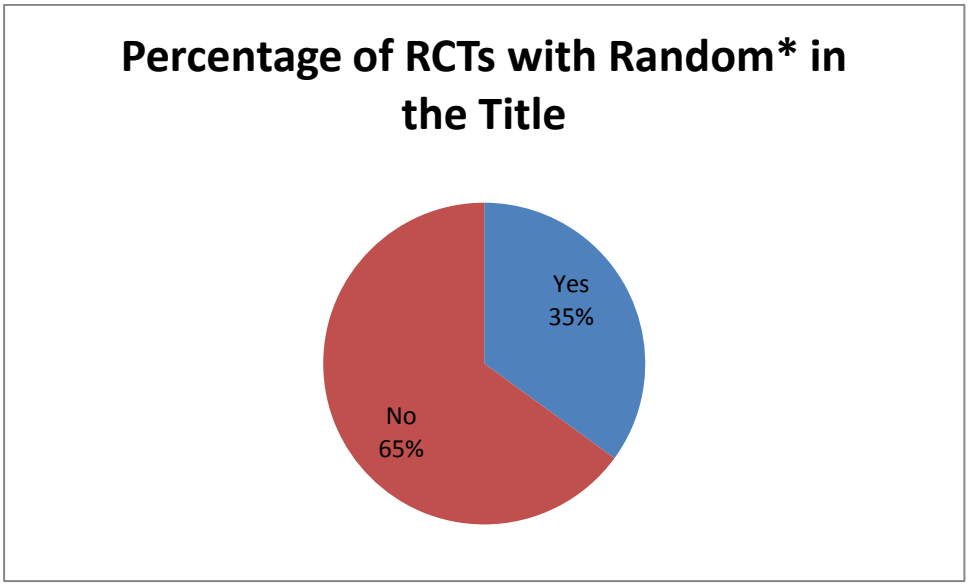


Table 5.15. Number of RCTs with random* in the title and ethical approval and informed consent or not.

Random* in title	Ethics and consent	Not ethics and consent
Yes	51 (66.2%)	26 (33.8%)
No	55 (39.2%)	86 (61.0%)
Overall	106 (48.6%)	112 (51.4%)

Random in Abstract but not Title*

Of the RCTs 167, (76.61%) had random in their abstract if not in the title, Figure 5.3. This was statistically associated ($p<0.001$) with the RCT having obtained ethical approval and informed consent. Of the RCTs that had random* in the abstract 92 (55.1%) had ethical approval and informed consent, whereas of those RCTs which did not have random* in the title or abstract, only 27.5% had ethical approval and informed consent, as seen in Table 5.16; Figure 5.14. This difference was statistically significant, (OR=3.24, 95% CI 1.63-6.44).

Figure 5.3. Percentage of RCTs with random* in the abstract but not title.

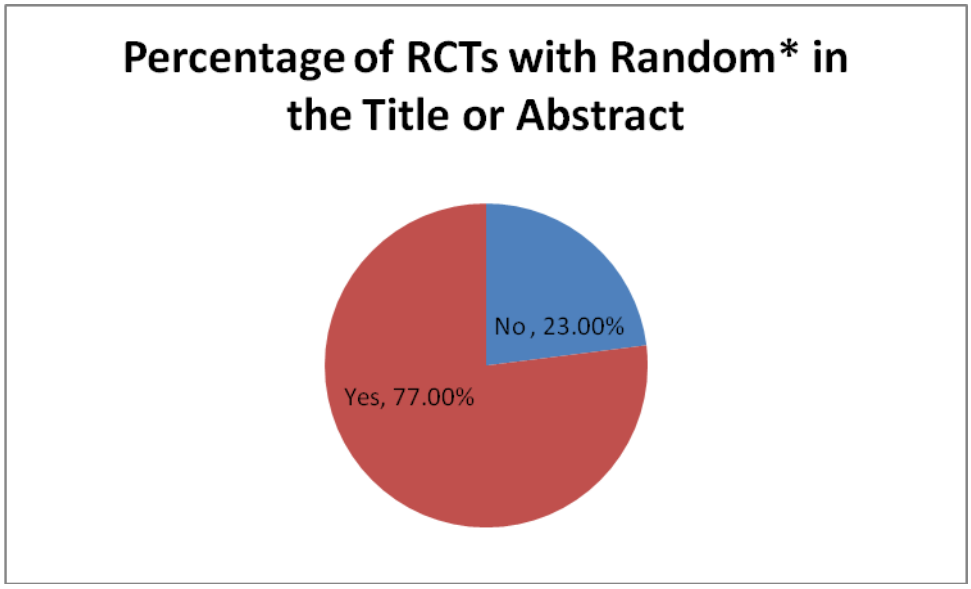


Table 5.16. Number of RCTs with random* in the abstract but not title with ethical approval and informed consent or not.

Random* in abstract but not title	Ethics and consent	Not ethics and consent
Yes	92 (55.1%)	75 (44.9%)
No	14 (27.5%)	37 (72.5%)
Overall	106 (48.6%)	112 (51.4%)

Random in the main body of the paper and not the title or abstract*

Of the 44 RCTs (20.2%) of RCTs had only had Random* in the main body of the paper and not the title or abstract, see Figure 5.4, thus 96.8% of RCTs (211 RCTs) had random* somewhere in the article, either the title, or abstract or body, see Table 5.17. There were seven RCTs in which the word random* did not appear. Of these four had ethical approval and informed consent, while three did not. This difference was not statistically significant, (OR=0.70, 95% CI 0.15-3.21).

Figure 5.4. Percentage of RCTs with random in the body of the article but not the title or abstract with ethical approval and informed consent or not.

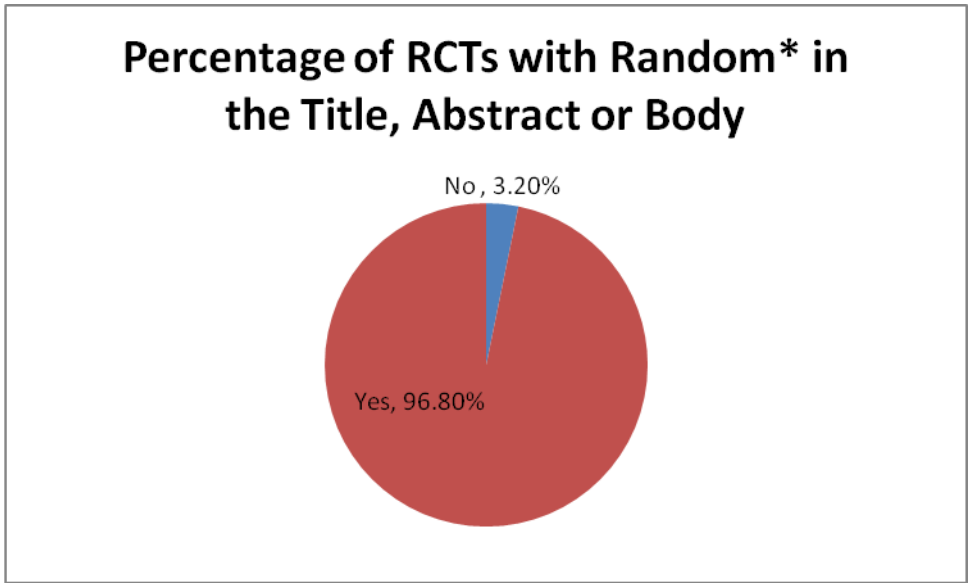


Table 5.17. Number of RCTs with random in the title or abstract or body of the article with ethical approval and informed consent or not.

Random* in title or abstract or body	Ethics and consent	Not ethics and consent
Yes	102 (48.3%)	109 (51.7%)
No	4 (57.1%)	3 (42.9%)
Overall	106 (48.6%)	112 (51.4%)

Logistical Regression

A logistical regression analysis was used to determine the association of various predictors to the liklihood of RCTs having obtained ethical approval and informed consent. See Appendix 3 for raw data.

The predictors examined initially were:

1. The journal the article was published in; namely the AJODO, AO, EJO or JO.
2. The number of author; 1-3, 4-6 or >6.
3. How many centres the RCT was performed in; 1, 2, $\geq$3.
4. The location of origin of the RCT; EU (excluding the UK), UK, USA or Other.
5. The involvement of a statistician; yes or no.
6. The year of publication; either between 2001 and 2005 inclusive or 2006 and 2010 inclusive.
7. Random* in the title; yes or no
8. Random* in the abstract, if not in the title; yes or no
9. Random* in the body of the article, if not in the title or abstract; yes or no.

Significant indictors of ethical approval and informed consent were the;

- The journal of publication ($p=0.004$)
- Number of authors ($p<0.001$)
- Number of centres ($p=0.008$)

- Location of origin (p=0.001)
- Year of publication (p=0.003)
- Random* in Title (p<0.001)
- Random* in Abstract not Title (p<0.001)

Indicators which did not reach statistically significant levels were:

- Involvement of a statistician (p=0.69)
- Random* in Body of article (p=0.65)

A logistic regression analysis showed the most significant indicators of ethical approval and informed consent to be:

- Publication in the JO (p=0.018)
- 6 or more authors (p<0.001)
- Random* in the abstract not title (p=0.004)
- Publication after 2004 (p=0.001).

5.6. Identification of RCTs

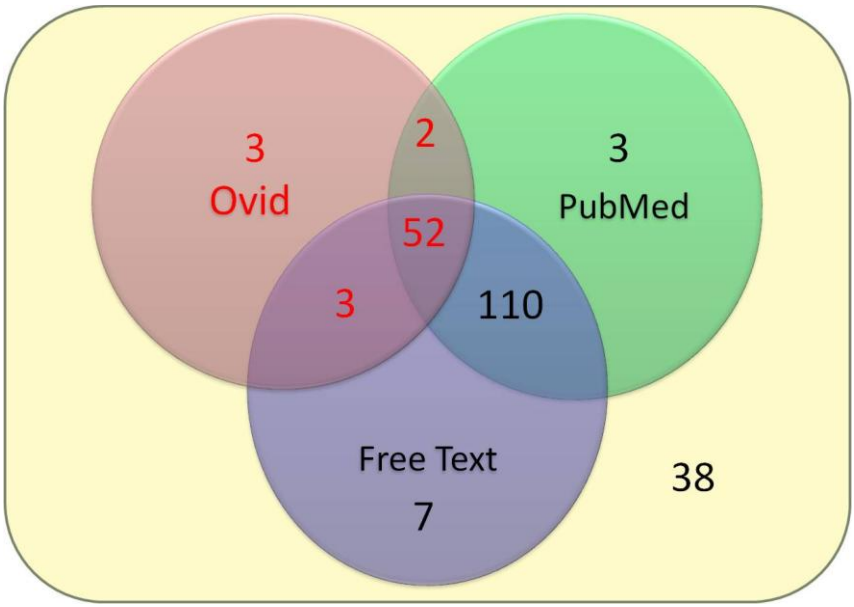
Hand-searching identified 218 RCTs which fulfilled Cochrane criteria and which were published in the AJODO, AO, EJO and JO between 01/01/2001 and 31/12/2010. Ovid located 61 RCTs and was the least accurate, failing to locate 157. PubMed found 167 RCTs, it missed 51 (23.4%) of the total RCT number. When compared to the gold standard of hand-searching, the free text search was the most sensitive, selecting 173 (79.4%), see Figure 5.15. However the specificity was low with 665 "RCTs" found. Ovid was significantly less sensitive than PubMed (OR 8.43, 95% CI 5.48, 12.97) missing 157 RCTs (72.0%), while PubMed missed 51 (23.4%) see Figure 5.16. The free text PubMed search, using the terms orthodontic AND random*, was the most sensitive missing 45 RCTs (20.6%) but this was not statistically significant (OR 0.85, 95%CI 0.54, 1.34) when compared with PubMed.

A combination of all three electronic search methods underestimated the number of RCTs compared to handsearching by 17%. 56 RCTs (25.7%) were found by all three electronic search methods, see Table 5.18; Figure 5.5.

Table 5.18. Number of RCTs found and missed by all search methods

Search Method	Found	Missed
Ovid	61	157
PubMed	167	51
Free Text	173	45
Handsearching	218	0

Figure 5.5. Number of RCTs found and missed by all three electronic search methods.



Chapter 6. Discussion.

The total number of RCTs and CCTs published in the AJODO, AO, EJO and JO from 1st January 2001 to 31st December 2010 was 218 and 89 respectively. This comprised a very small percentage of all articles published over the time period, with RCTs making up 4.6% of all articles published and CCTs contributing 1.9%.

CCTs

77.5% of all CCTs were published in the AJODO and AO combined with the JO publishing just one CCT over the ten year period. There was a low level of compliance with the Declaration of Helsinki, with 36% had both ethical approval and informed consent and 39.3% having neither. Ethical approval only was obtained by 8.7% of CCTs and informed consent only by 14.6%.

RCTs

There were 218 RCTs published. This was significantly more than the number of CCTs published (OR 2.5). 54.6% of all RCTs were published in the AJODO. Possible reasons for this are discussed later. The EJO published 20.6% of the RCTs, the AO 17.4% and the JO 7.3%. However, as a percentage of total number of articles published, the AJODO, EJO and JO all published approximately the same percentage of RCTs. 5.3% of AJODO articles, 5.1% of EJO articles and 5% of JO articles were RCTs. The AO published the lowest percentage of RCTs at 2.8%.

Compliance with the ethical approval and informed consent components of the Declaration of Helsinki was better with RCTs than CCTs although it was still well below the expected 100% compliance, as all trial reports involving human participants should include a statement

stating compliance with the Declaration of Helsinki. Of the 218 RCTs, 106 (48.6%) had both ethical approval and informed consent and 59 (27.1%) had neither. Ethical approval only was obtained by 32 (14.7%) of RCTs and informed consent only by 21 (9.6%). The authors of those RCTs which did not mention obtainment of either ethical approval or informed consent were contacted. Many of the email addresses provided in the article were not functioning. There was a very low response rate with only two authors responding (3.4%) and thus this was not investigated further. The RCTs were investigated with regards to various trial characteristics, along with whether these were associated with an increased likelihood of obtaining ethical approval and informed consent. These included the;

- Journal of publication
- Number of authors
- Number of centres the RCT was performed in
- Location of origin of the RCT
- Involvement of a statistician
- Year of publication
- Random* in the title
- Random* in the abstract, if not in the title
- Random* in the body of the article, if not in the title or abstract.

These trial characteristics were chosen once all the RCTs had been selected as these were characteristics which varied significantly between RCT reports. Other characteristics which could have been investigated may have included funding or journal impact factor.

Journal of publication

The journal in which the RCT was published had a significant impact on the likelihood of an RCT having obtained both ethical approval and informed consent, p=0.004. 12 of the 16 (75%) RCTs published on the JO had obtained both ethical approval and informed consent. The AO was the least compliant with only 10 (26.3%) of RCTs having obtained both. The AJODO, AO and EJO were broadly similar in the number of RCTs which had obtained neither ethical approval nor informed consent, this percentage ranged from 22.2% for the EJO to 36.8% for the AO. The overall average for RCTs having recorded both ethical approval and informed consent was 48.6%, but this belies a large range between different journals. Thus the journal had a statistically significant impact (p=0.004) on the probability of the RCTs published in different journals having obtained ethical approval and informed consent.

A significantly greater number of articles were published in the AJODO. This can be explained by a number of factors, including that fact that it publishes editions 12-13 times per year, in addition having a number of papers available online only. Its mean number of papers per issue is less than that of the AO at 18 for the AJODO versus the AO's 22. Despite this increased number of articles its percentage of RCTs was broadly similar to the EJO and JO and higher than the AO.

Why compliance was greater in the JO was not examined, however this may be due to the editorial policy, early adoption of the CONSORT Guidelines and a tighter refereeing process.

Number of authors

The number of authors was very statistically significantly associated (p<0.001) with the RCT having obtained both ethical approval and informed consent. Only 45.5% of RCTs with 1 to 3 authors had ethical approval and informed consent whereas 94.7% of RCTs with >6 authors fulfilled these criteria. This is perhaps due to the hypothesis that as more people are involved

it is more likely that at least one of the authors will consider it an important criteria to have fulfilled. This may perhaps be due to the trials with increasing numbers of authors being more likely to be multi-centre trials. Those funded by a government department or agency, for example the Medical Research Council in the UK, would insist on appropriate procedures being followed, especially with regards to the protection of the participants.

Number of centres the RCT was performed in

The number of centres the RCT was carried out in was also significant (p=0.008). Although the majority of RCTs were performed at single site centres (182), when RCTs were performed in 2 or more sites, they were much more likely to have obtained ethical approval and informed consent, 44% versus >88%. This may be explained by multicentre trials being larger and more likely to be in receipt of funding from external sources and thus the methodology is more closely supervised and associated with tighter processes.

Location of origin of the RCT

The location an RCT was based in had a significant impact on whether ethical approval and informed consent had been obtained (p=0.008). Research from the UK was analysed separately to that from the rest of the EU. This decision was made due to the disproportionately large volume of RCTs published by authors from the UK and it was felt this merited its own individual assessment. RCTs published by UK authors showed the highest level of compliance with the Declaration of Helsinki, namely that they have obtained both ethical approval and informed consent. RCTs published by UK authors had obtained both ethics and consent in 65.2% of cases, which along with the EU authors was the highest level.

There was a low level of both ethical approval and informed consent having been obtained by RCTs performed in the USA (29.3%). This may be due to a large number of American trials

being published in the AO which has a low level of compliance with ethical approval and informed consent. Another interesting feature, which was apparent on review of the literature, was that trials performed in the USA in particular are reported multiple times.[115,116,117, 118] It is generally, but not always, different aspects of these trials that were reported. This tendency to publish many articles from the same piece of research, or "salami slice" may be due in part to the need in academia to "publish or perish" and to ensure that funding authorities, universities or other stake holders in the research get the maximum amount of publications in ideally high impact journals.

Involvement of a statistician

The involvement of a statistician was not statistically significantly associated (p=0.86) with an RCT having both ethical approval and informed consent. When the exact position of the author was unclear, for example if it was stated only that they worked in the "Orthodontic Department" their name and university was searched online via Google to investigate if they were a statistician. This method is likely to underestimate the involvement of statisticians in this group of RCTs as not all the statisticians involved in the RCT are likely to either be an author or acknowledged. It is generally held that all people who make a meaningful contribution to the research should be listed as an author. This may make the process more transparent and in the case of the statistician, acknowledge the important role they play. Some journals, such as the JO, request that each author or contributor state their contribution to the research. This method could be adopted by all journals to ensure the involvement of a statistician and that each individual's role is acknowledged and recognised. Accurate statistical reporting and the use of appropriate statistical analyses, are becoming more crucial in the peer review process, with some journals involving statisticians as peer reviewers.

Year of publication

The year of publication was statistically significantly (p=0.002) associated with a paper having acquired ethical approval and informed consent. The time of publication was divided into two groups, 2001 to 2005 and 2006 to 2010. These dates were chosen as they divided the ten year time period into two and also because the European Clinical Trials Directive (ECTD) was published in 2004.This highlighted the importance of the academic communities' attention once more to the need for ethical approval and informed consent and standardised the procedure throughout the EU. The significance of these results suggests that the implementation of the ECDT had a positive effect on the conduct of trials. The differences between EU trials and the rest of the world could be investigated further.

*Random**

When handsearching the journals for RCTs it became apparent that contrary to the CONSORT Statement,[119] RCTs were not being published with "Randomised Controlled Trial" in the title. Thus each RCT was assessed as to whether it contained random* in the title, or the abstract if not the title, or body of the article if not the title or abstract. Random* was chosen to account for any differences in the spelling of randomised, for example randomized.

Random in the title*

Of the 218 RCTs found, only 77 (35.5%) had random* in the title. This has a significant impact on the selection of RCTs for systematic reviews via electronic search methods. If random* was in the title, this was strongly associated with the RCT having obtained both ethical approval and informed consent with p<0.001.

Although random* in the title or as a keyword is one of the CONSORT Guidelines, as is a statement confirming ethical approval and informed consent have been obtained. However

these guidelines do not appear to be widely followed in the reporting of orthodontic RCTs. Therefore perhaps those RCTs which have random* in the title are more likely to be written up as per CONSORT Guidelines and have recorded obtaining ethical approval and informed consent.

Random in the abstract, if not in the title*

167 (76.61%) RCTs had random in their abstract if not in the title. This was statistically associated ($p<0.001$) with the RCT having obtained ethical approval and informed consent. Of the RCTs which did not have random* in the title or abstract 72.5% did not have ethical approval and informed consent.

Stating the paper is an RCT, either directly in the title or by indirectly implying it, for example, by discussing the randomisation process is a feature that one whould expect most RCTs to adhere to. Those RCTs which do not contain this are perhaps poorly reported and may thus either not have obtained, or else fail to mention having obtained ethical approval and informed consent.

Random in the body of the article, if not in the title or abstract.*

Of the 218 RCTs, 44 (20.2%) had only Random* in the main body of the paper and not the title or abstract, thus 96.8% of RCTs (211 RCTs) had random* somewhere in the article, either the title, or abstract or body. There were 7 RCTs in which the word random* did not appear;. Of these 4 had ethical approval and informed consent and 3 did not. The likelihood of these RCTs being selected for a systematic review is extremely low as they require reading of the entire article and then clarification of the methodology in a separate article. This will significantly reduce their likelihood of being selected electronically for inclusion in, for example, a systematic review. If all RCTs on a particular topic are not included then there is a

risk of bias in that systematic review and thus in treatment effect being over or underestimated.

Significant indicators of ethical approval and informed consent

A logistic regression analysis (see Appendix 3) showed the most significant indicators of ethical approval and informed consent to be:

- Publication in the JO ($p=0.018$)
- 6 or more authors ($p<0.001$)
- Random* in the abstract not title ($p=0.004$)
- Publication after 2006 ($p=0.001$)

This showed that although the numbers of RCTs which were published in the JO or had 6 or more authors were small they were well reported ethically.

Identification of RCTs

When handsearching the journals for RCTs and CCTs it became apparent that contrary to the CONSORT Statement RCTs were not being published with "Randomised Controlled Trial" in the title. Thus each RCT was examined under the following criteria: whether it had RANDOM* in the title, abstract or main body of the paper.

These finding led to the hypothesis that due to lack of accurate labelling of RCTs electronic search engines, i.e. Ovid and PubMed would underestimate the number of RCTs on a topic, which would therefore bias the results of a systematic review in the subject.

Systematic reviews aim to select and appraise all high quality research relevant to a particular question. They are specifically designed to minimise bias, so as to produce the most reliable findings to most accurately inform decision making. Such reviews generally only include RCTs. If the systematic review fails to include all relevant RCTs, bias in estimating treatment effect will arise. It must be considered that systematic reviews are increasingly used for a variety of purposes,[120] such as by a grant agency to ensure that there is sufficient need for research in that particular area, by clinicians to keep up to date with their speciality, by journals to assess the merit in publishing research in an area [122] and, increasingly, in the development of clinical guidelines.[123, 124] For these aims to be achieved to a satisfactory degree, it is essential that systematic reviews accurately represent the body of research available for that particular subject.

This research demonstrates that the number of orthodontic RCTs in the literature is significantly underestimated by using electronic searching alone, either via free text searches or by publication type. Electronic searching is the main medium for trial selection for many systematic reviews including Cochrane.[6] It is likely that this underestimation of RCT

numbers is not confined to orthodontics or indeed dentistry as a whole. To improve the specificity of electronic searches journal editors should ensure that one of the keywords for RCTs is random and that, as per CONSORT Guidelines, RCTs are clearly identified in the title as such.

What do the findings mean?

Many reports of RCTs and CCTs do not comply with ethical guidelines. Each of the journals' guidelines to authors noted that a statement which confirms compliance with both ethical approval and informed consent should be contained within each submitted manuscript. This may be the case, however, these statements are not being published. This has implications for journals' referees and editors as it is they who have the final say on the wording of published articles and thus must ensure that such a statement is included in the finished manuscript. Also they must ensure that the editorial and reviewing process will not allow any research on human participants and more broadly on animals to be published if it has not reached the minimum ethical standards. Furthermore it important that any RCTs are correctly labeled as such and categorised accurately in online databases such as MEDLINE. This may be improved by providing a checklist for referees, this may help ensure that papers are rigourously assessed and subsequently categorized correctly.

Due to lack of compliance with the CONSORT Statement on reporting of RCTs, it is difficult to locate RCTs effectively and with acceptable specificity and sensitivity using electronic search methods. Handsearching was much more effective, however it is extremely time consuming and not regularly performed. However once handsearching has been done it does not need to be repeated if kept on a contemporaneous database. Thus, most searches for RCTs, for example for use in systematic reviews, compiling guidelines and arranging grant applications, are more likely to be performed by electronic searching. It is of concern that this research demonstrates an underestimation of RCT numbers by 17%, even when combining three different electronic search methods, as this could lead to significant bias in the aforementioned use of RCTs.

Although 218 RCTs are reported here, the actual number of RCTs is lower as many of these RCTs are the same trial reported more than once. Even when comparing the 218 RCTs to the total of 4847 published articles, this is extremely low and results in the evidence basis for orthodontics being less robust than ideal. It highlights the need for future RCTs in orthodontics and the importance of the correct categorization of these trials so their value in developing a strong evidence base for orthodontics can be maximized.

Multiple reporting of RCTs is particularly apparent in RCTs based in the USA, as discussed previously. This may be one of the reasons why journals such as the AJODO report more RCTs, though part of this is likely to be the AJODO's impact factor. Unfortunately, the JO does not have an impact factor, which may lead UK researchers to preferentially publish in the AJODO, AO or EJO rather than the JO.

Comparison with other studies

A review of five major medical journals, namely the BMJ, (International Edition), The Lancet (British Edition), Annals of Internal Medicine (Annals), the Journal of the American Medical Association (JAMA) and the New England Journal of Medicine (NEJM) which assessed all clinical research articles from 1st January 2005 to 31st December 2006 under the criteria of having obtained ethical approval and informed consent.[125] The results of this research was much more positive than that published in Orthodontics and Oral and Maxillofacial Surgery with only 3.2% of published clinical research not having recorded ethical approval, 5.5% not having recorded informed consent and 1.3% not having recorded either, as seen in Table 6.1. The variations seen over time and between different journals, as seen in the reporting of Orthodontic Clinical Trials, was also noted in this study.[125] Although this study looked only at a two year period, there was a statistically significant difference in

the incidence of failure to report ethical approval between 2005 and 2006 (p=0.005), the difference in failure to obtain consent between the two years was not significant (p=0.510). There were also statistically significant differences between the quality of ethical reporting between journals. RCTs were the best reported of the different research types and were least likely to be missing statements stating that ethical approval (p=0.001) and informed consent (0.005) had been obtained.

These journals had been investigated previously by Schroter.[126]

Table 6.1. Comparison of ethical approval and informed consent in different specialities.

Speciality	Incidence of reporting of ethical approval (number of articles)	Incidence of reporting of informed consent (number of articles)	Time period	Research type
Orthodontics	63.0% (138)	58.3%(127)	2001-2010	RCTs CCTs
Oral and Maxillofacial Surgery[111]	22.0% (118)	25.0% (135)	2005-2007	"All research involving human subjects"
General Medicine[125]	96.8% (1097)	94.5% (1071)	01/01/2005-31/12-2006	"All clinical research articles"
Anaesthetics[127]	71% (845)	66% (726)	2001	"All publications involving human participants"

Comparison with previous orthodontic research

Harrison's research[4] investigated the incidence of ethical approval and informed consent for RCTs and CCTs published between 1989 and 1998. 70 CCTs and 85 RCTs were published over the time period. She found that of the RCTs 17% had ethical approval and 34% stated informed consent had been obtained. Of the CCTs published 16% mentioned obtainment of ethical approval and 14% obtained informed consent. In total 11% of trial reports mentioned both ethics and consent. No statistically significant difference over time in the incidence of obtainment of ethical approval and informed consent was noted.

There were significant differences between the CCTs and RCTs published between 1989 to 1988 and 2001 to 2010.

The number of RCTs increased sharply from 85 to 218. There was a large improvement in the number of RCTs with ethical approval and informed consent from 17% to 63.3% and 34% to 58.3% respectively.

Of the CCTs, there was a similar number published over both time periods, with 85 between 1989 to 1998 and 89 between 2001 to 2010. Considering the large increase in RCT numbers the fact that there was not a corresponding increase in CCT numbers was surprising. This may perhaps be due to the strict criteria a CCT must fulfill to be classified as such by Cochrane. There was a large improvement in both ethical approval and informed consent over the time period, from 16% to 45% and 14% to 50.6% respectively.
Overall the number of trials with both ethical approval and informed consent increased from11% to 45%.

Within the 10 year period 2001-2010 there was a statistically significant difference in the number of RCTs with ethical approval and informed consent published between 2001 to 2005 and 2006-2010. Those RCTs published in 2006 or later were better reported ethically with 57% having ethics and consent compared to 36.7% of those published between 2001 to 2005 (OR=2.29, 95% CI 1.32, 3.99).

The improvements in reporting of ethical approval and informed consent fits in with the other available literature showing that reporting of these important criteria is improving over time.

Generalisability

The results of this study are probably only applicable to orthodontics in terms of the compliance of RCTs and CCTs with ethical approval and informed consent. This is because there appears to be a large amount of variation in compliance with ethical approval and informed consent between various specialities, as seen in Table 6.1. Despite this the CONSORT Statement is an evidence-based minimum set of recommendations for reporting RCTs, thus all RCTs should be reported according to it across all dental and medical specialities, therefore for full compliance all RCTs across all specialities would have confirmation of obtainment of ethical approval and informed consent.

The Cochrane Handsearching course is also applicable to all healthcare trials and its findings derived from handsearching following this protocol are also generalisable. The finding that electronic searching is less sensitive at locating RCTs than handsearching is likely to be generalisable across different specialities and has been previously proven in other spheres of medicine, see Table 6.2.

Table 6.2. Comparison of electronic searching versus handsearching in other medical specialities.

Comparison	Subject	Result
Electronic searching V Handsearching	Cochrane[133]	Handsearching 92-100% MEDLINE 55%, EMBASE 49% and PyscINFO 67%.
MEDLINE V Handsearching	Mental Health Care[134]	MEDLINE 52% (CI 48-56%) Handsearching 94% (CI 93-95%)

Limitations of the study

Handsearching

The handsearching method followed was that of the Cochrane Collaboration. This was originally instigated to form the Cochrane CENTRAL Register of Controlled Trials which is the Cochrane Collaboration's source of trial reports. This lays down strict criteria for the classification of RCTs and CCTs. Due to the strictness of these criteria and the inherent risk of missing trials due to inaccurate searching, there is a risk that the number of trials included may be incorrect and therefore produce biased results. This was assessed by a pilot study and checking intra-examiner reliability which was high. Although there are risks of introducing biases with handsearching it was found to be a far superior method of RCT selection compared to various methods of electronic searching.

Handsearching depended on information provided by authors. In some RCTs, ethical approval and informed consent were not mentioned by the author. The authors of these RCTs were contacted as it was felt that the results could be potentially biased if the authors had actually obtained both ethics and consent but had inadvertently left out this fact. However, despite numerous attempts to contact authors, the response rate was extremely low (3.6%) and therefore this was considered to be probably insignificant. Many of the email addresses provided in the article were not functioning, even those provided recently, and perhaps it is an important role of the journal to ensure that authors are contactable with accurate functioning contact details. Perhaps it would be better to have the contact details of the supervising author who are perhaps likely to be in the Department for a longer period of time, rather than, for example a Specialist Registrar. There is little evidence on whether such papers are likely to have ethical approval and informed consent or not, it has been investigated by Perkins in dermatology.[128] This paper contacted all authors who submitted

their research on human participants for publication in the Journal of the American Academy of Dermatology (JAAD) and had failed to mention ethical approval or informed consent. Out of the original 150 submitted studies, 36% (n=54) did not mention ethical approval in the first instance. 15% (n=22) mentioned consent but not ethics. The authors of 42 of these papers which did not mention ethics were contacted by editorial staff, the remaining papers were not considered suitable for inclusion in the journal, thus potentially biasing the outcome of this particular study. Of those 42 papers which were being considered, the authors were then contacted for clarification of the ethical status of their research. 20 (48%) of the papers were returned with the required information and 3 papers confirmed their exemption from the ethical approval process. However the remaining papers were either withdrawn (n=9), not resubmitted (n=5) or acknowledged to be lacking in ethical review (n=5). When contacted by editorial staff there was a relatively good response rate, however this may be subject to bias due to the high proportion of papers which were not considered suitable for inclusion in the journal whose authors were not contacted and the high number of papers which were then withdrawn, or not resubmitted, when clarification on their ethical status was sought. A percentage of these papers may not have had ethical approval but it is unfortunately not possible to tell what percentage. The difference in response rate may be due to the fact that the authors of the orthodontic papers had already had their research published whereas those prospective dermatology authors had to reply to the journal editor to have their research considered for publication.

Identification of Papers

This was a retrospective study which, by its nature, was open to bias. All papers published within the four main orthodontic journals over the ten year period were handsearched to identify RCTs and CCTs. It is possible mistakes were made due to human error and articles which should have been included in the sample were omitted. This is made more likely due to

the poor titling of the RCTs which makes them more difficult to identify. Conversely, some studies which were neither a RCT nor CCT may have inadvertently been included. All precautions possible were taken to avoid this, this was checked by researching a random sample of 10% of the journals which demonstrated good intra-examiner reliability.

As electronic searching was carried out by three different methods it was thought that this would also aid in assessing handsearching reliability as it may have located additional RCTs which were missed by handsearching. However, no additional RCTs were found.

Sample size

The original sample size was based on Harrison's work[4] and a similar article published in Oral and Maxillofacial surgery[111] both of which showed an approximate doubling in the incidence of reported ethical approval and informed consent over the time period examined. The necessary sample size at 90% power would have been 177 trials. Instead it was decided to include all RCTs and CCTs which were found during handsearching, thus by including all relevant trials it was hoped that this would reduce bias.

Quality

During the data collection process, no attempts were made to assess the quality of the individual trials, for example, how the RCTs were randomised or blinded. It was thought to be outside the remit of this study to assess this, this will ideally be analysed at a later date. Previous research in this area has shown that these criteria are inadequately reported.[129] Previous work assessing the quality of published RCTs by the Cochrane Collaboration has identified a lack of methodological rigour or clarity in some RCTs which has resulted in their exclusion from systematic reviews.[129] A paper by Tuech *et al* assessed and compared the methodological quality and ethical quality of all Stage III cancer RCTs published in ten journals over a three year period.[130] This paper found an association between methodological

and ethical quality, perhaps showing closer attention to all aspects of the research process. This was also seen in the orthodontic research examined where larger trials with more authors and centres appeared to comply better with ethical guidelines, possibly as these trials are planned and performed to a higher standard. Compliance with the CONSORT Statement is considered to be indicative of a high quality, well reported RCT. For RCTs to be written up in such a format it is important that journals engage with this Statement and request that RCTs are written up in such a format. This is not the case yet with 38% (n=62/165) of high impact medical journals mentioning the CONSORT Statement in their "Instructions to Authors", of these 62, 37% (n=23/62) stated in was a requirement and the remaining 63% (n=39/62) were less clear.[131]

Implications for Practice

Clinical

The main implication for practice is that this research indicates that electronic searching significantly underestimates the number of RCTs located. Even by combining three electronic search methods, 17% of RCTs were not located. Thus systematic reviews, based on this cohort of RCTs, may be subject to treatment effect bias and what we consider to be the best evidence, namely the systematic review, may be significantly biased.

Research

This research shows the importance of accurately labelling and classifying RCTs, both by including "randomised controlled trial" in their title, as per CONSORT Guidelines, so that they can be located during electronic searching and ensuring they are accurately classified in MEDLINE to ensure they can be located by PubMed or Ovid.

With respect to trials having reported ethical approval and informed consent, it is important that the editors ensure that these trials have obtained these ethical criteria and a statement conforming this is within the article.

In light of the difficulty contacting the authors of those RCTs without ethical approval and informed consent perhaps there should be a requirement to inform the journal of any changes to contact details and to ensure that they are functioning in the first place. Or perhaps the contact author should be the most senior author as they are likely to be the most stable person and remain working in the same department for the longest period of time, rather than, for example, a Specialist Registrar.

Further Research

- It has been shown in medicine that all RCTs are not included in systematic reviews,[132] and that this may bias the results of the systematic reviews. It would be interesting to take a selection of systematic reviews and assess whether they had included all relevant RCTs and compare these to Cochrane systematic reviews which also include handsearching.

- On searching the orthodontic literature much "salami-slicing" was apparent, with some extremely similar articles being published by the same research team. This was also obvious in the reporting of RCTs with the results of some RCTs and CCTs being sliced up and published in a number of papers. It appeared that there was a geographic divide in this regard. This would be worth investigating further, along with the multiple reporting of laboratory based research.

- Lack of recorded registration of animal trials also appears widespread in the orthodontic literature and could be researched in a similar way.

- This research should be repeated in approximately another decade to assess whether the rate of reporting of ethical approval and informed consent continues to improve.

- Assessment of the quality of RCTs published within these four main orthodontic journals in relation to CONSORT Guidelines.

Chapter 7: Conclusions

- There were 218 RCTs and 89 CCTs published in the AJODO, AO, EJO and JO between 2001 and 2010.

- Of the 89 CCTs reported, 32 (36%) had both ethical approval and informed consent, 36 (40.4%) had neither and 21 (23.6%) had either ethical approval or informed consent. Of the 218 RCTs reported, 106 (48.6%) had both ethical approval and informed consent, 59 (27.1%) had neither and 53 (24.1%) had either ethical approval or informed consent.

- Attempts were made to contact the authors whose RCTs did not mention either ethical approval or informed consent. However there was a very low response rate of two authors, (4.6%), so this was considered insignificant.

- Significant indicators of an RCT having obtained both ethical approval and informed consent were; the number of authors, random* in the title, random* in the abstract not title, location of origin, year of publication, journal of publication and number of centres. Of these publication in the JO, 6 or more authors, random* in the abstract not title and publication after 2006 were the most significant.

- Handsearching was more sensitive in the selection of RCTs than electronic searching. When combining three methods of electronic searching, namely MEDLINE via Ovid, publication type "RCT", MEDLINE via PubMed, publication type "RCT" and PubMed Free Text search for "orthodontic" AND "random*" 38 (17%) of RCTs were not found by any of the three electronic search methods.

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Appendix 1. Cochrane Collaboration Glossary Definitions.

Clinical Trial

"An experiment to compare the effects of two or more healthcare intervention. Clinical trial is an umbrella term for a variety of designs of healthcare trials, including uncontrolled trials, controlled trials and randomised controlled trials (also called Intervention Study). "[109]

Controlled Clinical Trial (CCT)

"Indexing term used in MEDLINE and CENTRAL. Within CENTRAL it refers to trials using quasi-randomisation, or trials where double blinding was used but randomisation was not mentioned."[109]

Randomised controlled trial (RCT)

An experiment in which two or more interventions, possibly including a control intervention or no intervention, are compared by being randomly allocated to participants. In most trials one intervention is assigned to each individual but sometimes assignment is to defined groups of individuals (for example in a household) or interventions are assigned within individuals (for example, in different orders or to different parts of the body).[109]

Appendix 2. Samples of emails sent to authors.

Sample Email

Sent: Fitzgerald Rhian (ROYAL LIVERPOOL AND BROADGREEN UNIVERSITY HOSPITALS NHS TRUST) [rhian.fitzgerald@nhs.net]

To: Anna-Sofia Silvola

Subject: Early headgear effects on the eruption pattern of maxillary canines

Dear Dr Silvola,

I am conducting a doctorate on the levels of ethical approval and informed consent in orthodontic RCTs. I would be grateful if you would answer the following questions on your May 2009 Angle Orthodontist article on the effect of early headgear.

All responses will be treated with utmost confidentiality.

1. Has your research obtained ethical approval and or informed consent?

2. If no, why not?

3. If yes, why was a statement to that effect not included in the published paper?

Thank you very much for your help. If you have any queries please do not hesitate to contact me.

Kind Regards,

Rhian Fitzgerald,

Specialist Registrar in Orthodontics

University of Liverpool

Sample Response

Dear Dr. Rhian Fitzgerald,

1. The study was initiated 25 years ago, and at that time a written informed consent was obtained from the parents with signature, this is archived.
2. At that time this procedure in Finland was considered sufficient by the principal investigator, Dr. Kantomaa.
3. This is published earlier in the papers concerning the same patient material

   "Informed consent was obtained from the parents

   before the randomization. To conceal the allocation, most practitioners who performed the treatment were not given information concerning the aim or rationale of the study. "Long-term soft-tissue response to orthodontic treatment with early cervical headgear--a randomized study.Virkkula T, Kantomaa T, Julku J, Pirttiniemi P.Am J Orthod Dentofacial Orthop. 2009 May;135(5):586-96.

   Best wishes,

   Pertti Pirttiniemi, Professor and Chair,

   Dpt. of Oral Development and Orthodontics,

   Dean of Faculty,

   Institute of Dentistry,

   P.O.Box 5281,

   FI-90014 University of Oulu, Finland

   +358-8-5375491

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   fax:+358-8-5375503

Appendix 3. Raw data for Logistical Regression.

Case Processing Summary

Unweighted Cases[a]		N	Percent
Selected Cases	Included in Analysis	218	100.0
	Missing Cases	0	.0
	Total	218	100.0
Unselected Cases		0	.0
Total		218	100.0

a. If weight is in effect, see classification table for the total number of cases.

Dependent Variable Encoding

Original Value	Internal Value
dimension0 No	0
Yes	1

Categorical Variables Codings

			Parameter coding		
		Frequency	(1)	(2)	(3)
journal2	AJODO	119	.000	.000	.000
	AO	38	1.000	.000	.000
	EJO	45	.000	1.000	.000
	JO	16	.000	.000	1.000
country2	EU	40	.000	.000	.000
	OTHER	71	1.000	.000	.000
	UK	66	.000	1.000	.000
	USA	41	.000	.000	1.000
numberauthors2	1-3	77	.000	.000	
	4-6	122	1.000	.000	
	7+	19	.000	1.000	
numcentres2	1	182	.000	.000	
	2	22	1.000	.000	
	3+	14	.000	1.000	
randomtitle2	NO	141	.000		
	YES	77	1.000		
randomabstract2	NO	51	.000		
	YES	167	1.000		
year2	2005 or before	90	.000		
	2006 or later	128	1.000		

Block 0: Beginning Block

Classification Table[a,b]

Observed			Predicted		
			ethicsandconsent		Percentage Correct
			No	Yes	
Step 0	ethicsandconsent	No	112	0	100.0
		Yes	106	0	.0
	Overall Percentage				51.4

a. Constant is included in the model.

b. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 0	Constant	-.055	.136	.165	1	.685	.946

Variables not in the Equation

			Score	df	Sig.
Step 0	Variables	journal2	13.536	3	.004
		journal2(1)	9.168	1	.002
		journal2(2)	1.902	1	.168
		journal2(3)	4.809	1	.028
		numberauthors2	17.794	2	.000
		numberauthors2(1)	2.977	1	.084
		numberauthors2(2)	17.717	1	.000
		country2	15.736	3	.001
		country2(1)	2.550	1	.110
		country2(2)	10.351	1	.001
		country2(3)	7.573	1	.006
		numcentres2	9.618	2	.008
		numcentres2(1)	5.691	1	.017
		numcentres2(2)	3.115	1	.078
		randomtitle2(1)	14.779	1	.000
		randomabstract2(1)	11.947	1	.001
		year2(1)	8.773	1	.003
	Overall Statistics		51.589	13	.000

Block 1: Method = Forward Stepwise (Likelihood Ratio)

Omnibus Tests of Model Coefficients

		Chi-square	Df	Sig.
Step 1	Step	14.972	1	.000
	Block	14.972	1	.000
	Model	14.972	1	.000
Step 2	Step	16.812	2	.000
	Block	31.784	3	.000
	Model	31.784	3	.000
Step 3	Step	5.677	1	.017
	Block	37.461	4	.000
	Model	37.461	4	.000
Step 4	Step	6.440	1	.011
	Block	43.901	5	.000
	Model	43.901	5	.000
Step 5[a]	Step	-2.277	1	.131
	Block	41.624	4	.000
	Model	41.624	4	.000
Step 6	Step	10.084	3	.018
	Block	51.708	7	.000
	Model	51.708	7	.000

a. A negative Chi-squares value indicates that the Chi-squares value has decreased from the previous step.

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	287.075[a]	.066	.089
2	270.263[b]	.136	.181
3	264.586[b]	.158	.211
4	258.146[b]	.182	.243
5	260.423[b]	.174	.232
6	250.339[b]	.211	.282

a. Estimation terminated at iteration number 3 because parameter estimates changed by less than .001.
b. Estimation terminated at iteration number 6 because parameter estimates changed by less than .001.

Classification Table[a]

Observed			Predicted		
			ethicsandconsent		Percentage Correct
			No	Yes	
Step 1	ethicsandconsent	No	86	26	76.8
		Yes	55	51	48.1
	Overall Percentage				62.8
Step 2	ethicsandconsent	No	86	26	76.8
		Yes	48	58	54.7
	Overall Percentage				66.1
Step 3	ethicsandconsent	No	87	25	77.7
		Yes	48	58	54.7
	Overall Percentage				66.5
Step 4	ethicsandconsent	No	73	39	65.2
		Yes	37	69	65.1
	Overall Percentage				65.1
Step 5	ethicsandconsent	No	73	39	65.2
		Yes	37	69	65.1
	Overall Percentage				65.1
Step 6	ethicsandconsent	No	79	33	70.5
		Yes	37	69	65.1
	Overall Percentage				67.9

a. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	randomtitle2(1)	1.121	.296	14.293	1	.000	3.067
	Constant	-.447	.173	6.703	1	.010	.640
Step 2[b]	numberauthors2			7.906	2	.019	
	numberauthors2(1)	-.045	.301	.023	1	.880	.956
	numberauthors2(2)	2.905	1.061	7.505	1	.006	18.273
	randomtitle2(1)	.993	.308	10.409	1	.001	2.700
	Constant	-.535	.259	4.258	1	.039	.585
Step 3[c]	numberauthors2			8.295	2	.016	
	numberauthors2(1)	-.028	.305	.008	1	.927	.972
	numberauthors2(2)	3.022	1.072	7.941	1	.005	20.527
	randomtitle2(1)	.714	.329	4.721	1	.030	2.042
	randomabstract2(1)	.910	.394	5.336	1	.021	2.485
	Constant	-1.165	.389	8.975	1	.003	.312
Step 4[d]	numberauthors2			8.372	2	.015	
	numberauthors2(1)	-.036	.310	.013	1	.909	.965
	numberauthors2(2)	3.045	1.077	7.990	1	.005	21.012
	randomtitle2(1)	.517	.343	2.275	1	.131	1.678
	randomabstract2(1)	1.004	.404	6.186	1	.013	2.730
	year2(1)	.788	.314	6.306	1	.012	2.199
	Constant	-1.637	.443	13.679	1	.000	.195
Step 5[d]	numberauthors2			9.223	2	.010	
	numberauthors2(1)	-.051	.308	.027	1	.869	.950
	numberauthors2(2)	3.171	1.073	8.739	1	.003	23.841
	randomabstract2(1)	1.227	.379	10.499	1	.001	3.412
	year2(1)	.899	.305	8.659	1	.003	2.457
	Constant	-1.697	.444	14.608	1	.000	.183
Step 6[e]	journal2			9.248	3	.026	
	journal2(1)	-.701	.450	2.432	1	.119	.496
	journal2(2)	.531	.394	1.813	1	.178	1.701
	journal2(3)	1.294	.668	3.756	1	.053	3.648
	numberauthors2			8.691	2	.013	
	numberauthors2(1)	.115	.326	.125	1	.724	1.122
	numberauthors2(2)	3.182	1.082	8.642	1	.003	24.099
	randomabstract2(1)	1.080	.392	7.602	1	.006	2.946
	year2(1)	1.000	.317	9.942	1	.002	2.718
	Constant	-1.825	.507	12.986	1	.000	.161

a. Variable(s) entered on step 1: randomtitle2.

b. Variable(s) entered on step 2: numberauthors2.
c. Variable(s) entered on step 3: randomabstract2.
d. Variable(s) entered on step 4: year2.
e. Variable(s) entered on step 6: journal2.

Variables in the Equation

		95% C.I.for EXP(B)	
		Lower	Upper
Step 1[a]	randomtitle2(1)	1.716	5.484
	Constant		
Step 2[b]	numberauthors2		
	numberauthors2(1)	.530	1.724
	numberauthors2(2)	2.286	146.069
	randomtitle2(1)	1.477	4.937
	Constant		
Step 3[c]	numberauthors2		
	numberauthors2(1)	.535	1.768
	numberauthors2(2)	2.509	167.922
	randomtitle2(1)	1.072	3.889
	randomabstract2(1)	1.148	5.381
	Constant		
Step 4[d]	numberauthors2		
	numberauthors2(1)	.526	1.772
	numberauthors2(2)	2.544	173.555
	randomtitle2(1)	.856	3.287
	randomabstract2(1)	1.237	6.024
	year2(1)	1.189	4.067
	Constant		
Step 5[d]	numberauthors2		
	numberauthors2(1)	.520	1.738
	numberauthors2(2)	2.912	195.207
	randomabstract2(1)	1.624	7.168
	year2(1)	1.350	4.471
	Constant		
Step 6[e]	journal2		
	journal2(1)	.205	1.197
	journal2(2)	.785	3.683
	journal2(3)	.985	13.503
	numberauthors2		
	numberauthors2(1)	.592	2.128
	numberauthors2(2)	2.888	201.101

	randomabstract2(1)	1.367	6.349
	year2(1)	1.460	5.061
	Constant		

a. Variable(s) entered on step 1: randomtitle2.
b. Variable(s) entered on step 2: numberauthors2.
c. Variable(s) entered on step 3: randomabstract2.
d. Variable(s) entered on step 4: year2.
e. Variable(s) entered on step 6: journal2.

Model if Term Removed

Variable		Model Log Likelihood	Change in -2 Log Likelihood	df	Sig. of the Change
Step 1	randomtitle2	-151.024	14.972	1	.000
Step 2	numberauthors2	-143.537	16.812	2	.000
	randomtitle2	-140.483	10.703	1	.001
Step 3	numberauthors2	-141.072	17.559	2	.000
	randomtitle2	-134.689	4.793	1	.029
	randomabstract2	-135.131	5.677	1	.017
Step 4	numberauthors2	-137.931	17.716	2	.000
	randomtitle2	-130.212	2.277	1	.131
	randomabstract2	-132.394	6.642	1	.010
	year2	-132.293	6.440	1	.011
Step 5	numberauthors2	-140.401	20.379	2	.000
	randomabstract2	-136.031	11.638	1	.001
	year2	-134.689	8.956	1	.003
Step 6	journal2	-130.212	10.084	3	.018
	numberauthors2	-134.401	18.462	2	.000
	randomabstract2	-129.271	8.203	1	.004
	year2	-130.378	10.416	1	.001

Variables not in the Equation

			Score	df	Sig.
Step 1	Variables	journal2	7.799	3	.050
		journal2(1)	5.852	1	.016
		journal2(2)	1.519	1	.218
		journal2(3)	1.581	1	.209
		numberauthors2	13.955	2	.001
		numberauthors2(1)	1.967	1	.161
		numberauthors2(2)	13.929	1	.000
		country2	7.137	3	.068
		country2(1)	.369	1	.543
		country2(2)	3.487	1	.062
		country2(3)	4.222	1	.040
		numcentres2	4.664	2	.097
		numcentres2(1)	2.595	1	.107
		numcentres2(2)	1.491	1	.222
		randomabstract2(1)	4.814	1	.028
		year2(1)	5.513	1	.019
	Overall Statistics		39.611	12	.000
Step 2	Variables	journal2	6.983	3	.072
		journal2(1)	4.885	1	.027
		journal2(2)	1.244	1	.265
		journal2(3)	1.821	1	.177
		country2	6.859	3	.077
		country2(1)	.033	1	.856
		country2(2)	2.377	1	.123
		country2(3)	5.098	1	.024
		numcentres2	3.470	2	.176
		numcentres2(1)	3.365	1	.067
		numcentres2(2)	.030	1	.863
		randomabstract2(1)	5.495	1	.019
		year2(1)	5.479	1	.019
	Overall Statistics		27.059	10	.003
Step 3	Variables	journal2	6.198	3	.102
		journal2(1)	3.698	1	.054
		journal2(2)	1.482	1	.223
		journal2(3)	1.791	1	.181

		country2	6.717	3	.081
		country2(1)	.095	1	.758
		country2(2)	1.389	1	.239
		country2(3)	6.072	1	.014
		numcentres2	2.459	2	.292
		numcentres2(1)	2.430	1	.119
		numcentres2(2)	.001	1	.977
		year2(1)	6.424	1	.011
	Overall Statistics		21.782	9	.010
Step 4	Variables	journal2	8.099	3	.044
		journal2(1)	4.219	1	.040
		journal2(2)	1.882	1	.170
		journal2(3)	2.792	1	.095
		country2	7.095	3	.069
		country2(1)	.050	1	.823
		country2(2)	2.485	1	.115
		country2(3)	5.257	1	.022
		numcentres2	2.099	2	.350
		numcentres2(1)	1.728	1	.189
		numcentres2(2)	.258	1	.612
	Overall Statistics		15.755	8	.046
Step 5[a]	Variables	journal2	9.802	3	.020
		journal2(1)	4.840	1	.028
		journal2(2)	2.150	1	.143
		journal2(3)	4.032	1	.045
		country2	9.030	3	.029
		country2(1)	.305	1	.581
		country2(2)	3.870	1	.049
		country2(3)	6.391	1	.011
		numcentres2	2.720	2	.257
		numcentres2(1)	2.266	1	.132
		numcentres2(2)	.316	1	.574
		randomtitle2(1)	2.291	1	.130
	Overall Statistics		17.950	9	.036
Step 6[a]	Variables	country2	6.591	3	.086
		country2(1)	.002	1	.963
		country2(2)	.958	1	.328
		country2(3)	5.448	1	.020
		numcentres2	2.618	2	.270

numcentres2(1)	1.964	1	.161
numcentres2(2)	.490	1	.484
randomtitle2(1)	.498	1	.480
Overall Statistics	8.317	6	.216

a. Variable(s) removed on step 5: randomtitle2.

Appendix 4. Additional Figures for Results

Figure 1. RCTs with ethical approval and informed consent

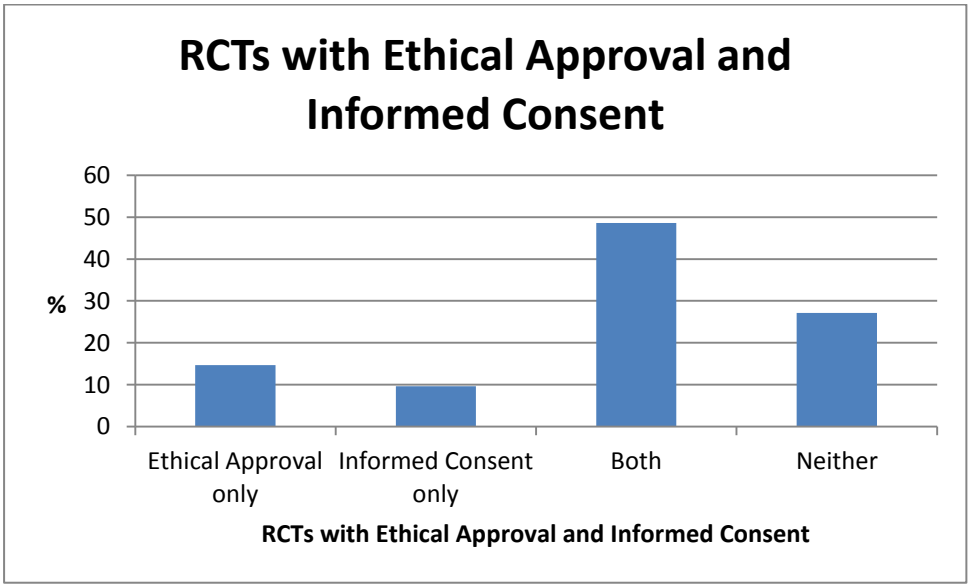


Figure 2. Percentage of CCTs with ethical approval and informed consent.

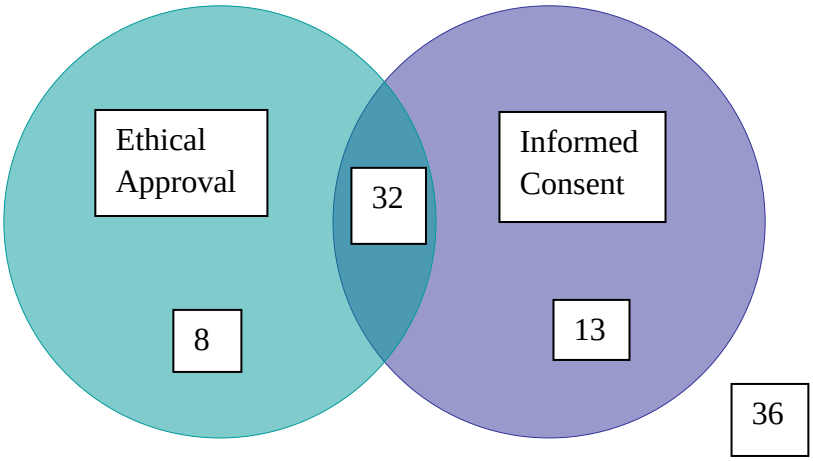
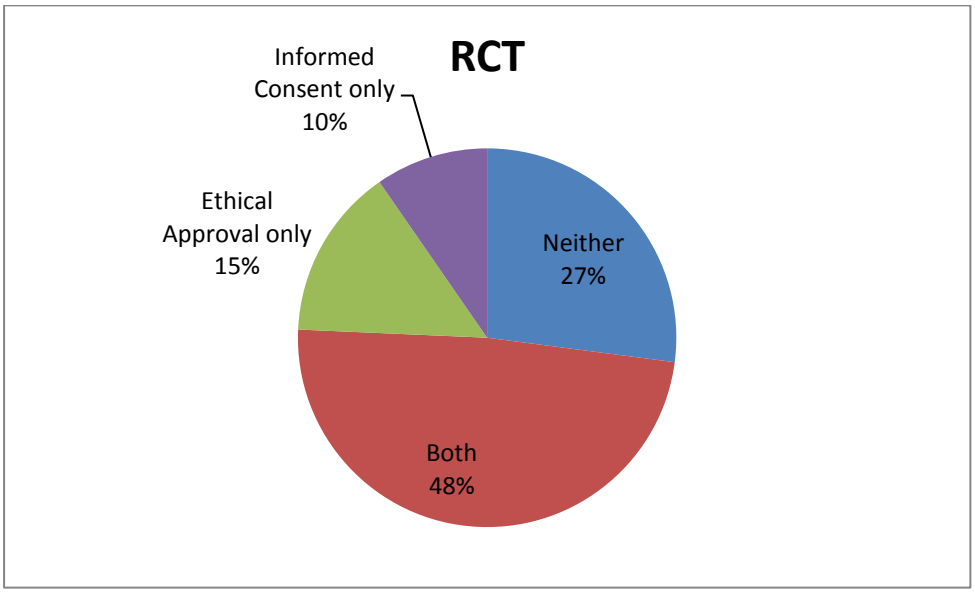


Figure 3. Percentage of RCTs and CCTs with ethical approval and informed consent.



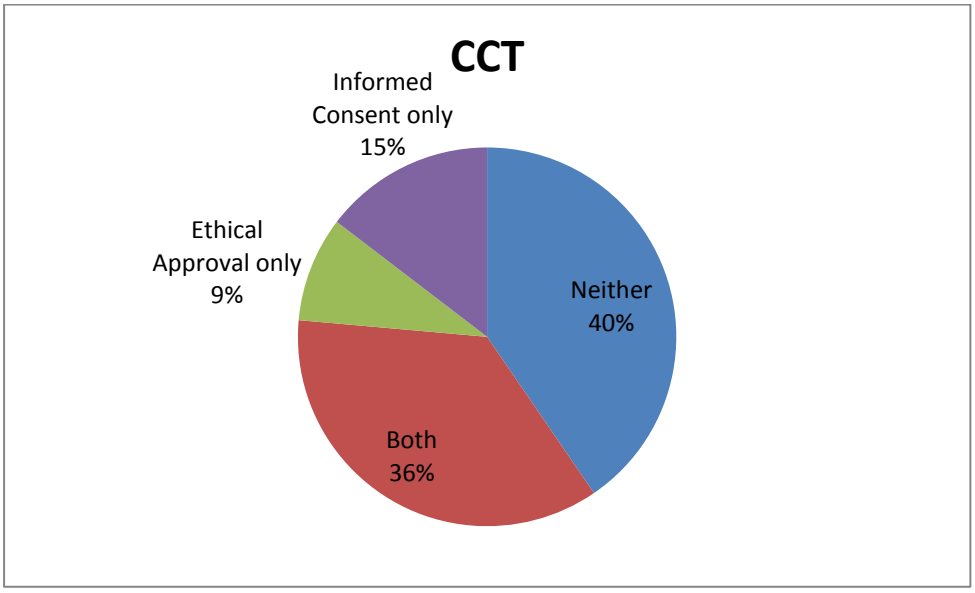


Figure 4. Journal of Publication and percentage of RCTs with ethical approval and informed consent or not.

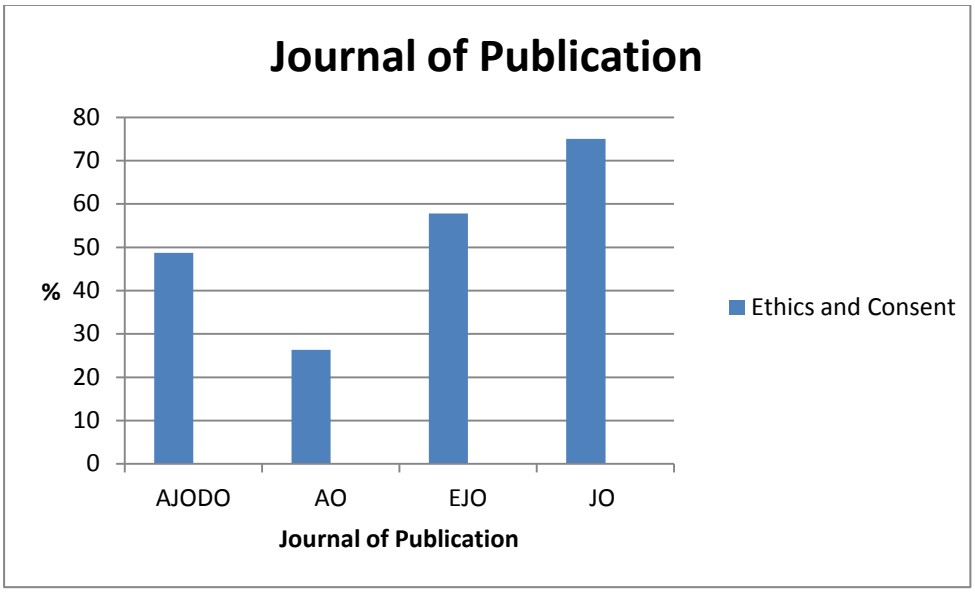


Figure 5. Number of Authors and percentage of RCTs with ethical approval and informed consent or not.

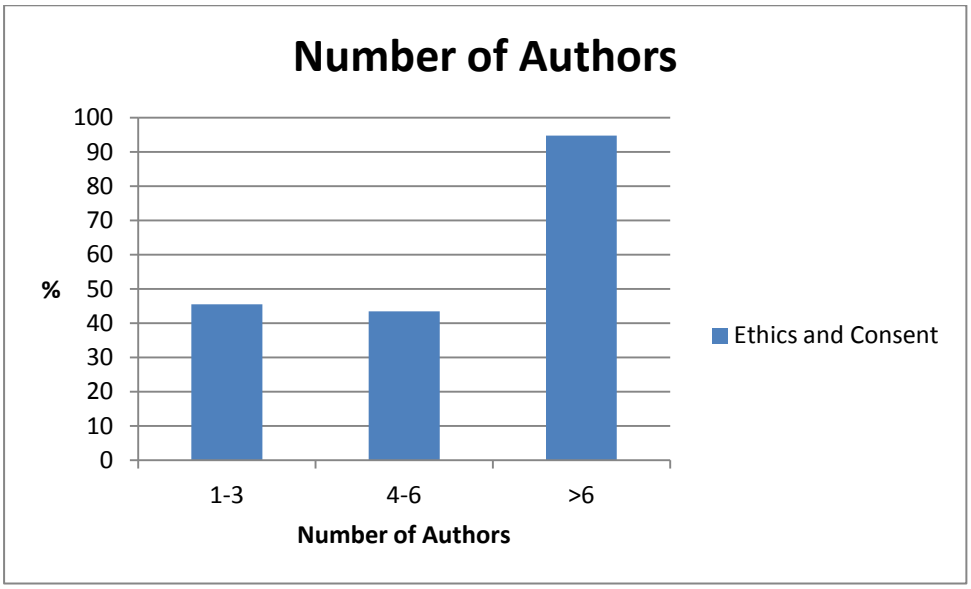


Figure 6. Number of Centres and percentage of RCTs with ethical approval and informed consent or not.

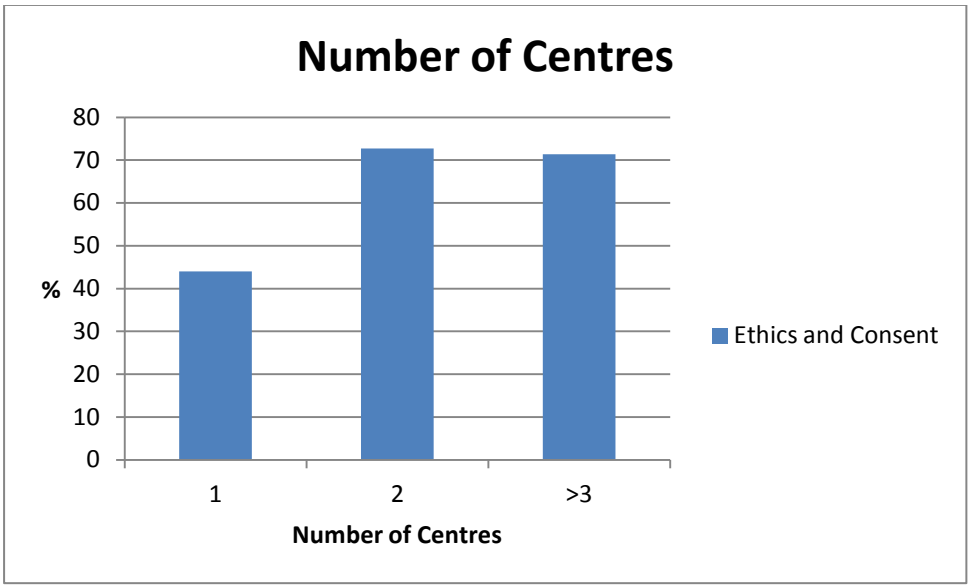


Figure 7. Location of Origin and percentage of RCTs with ethical approval and informed consent or not.

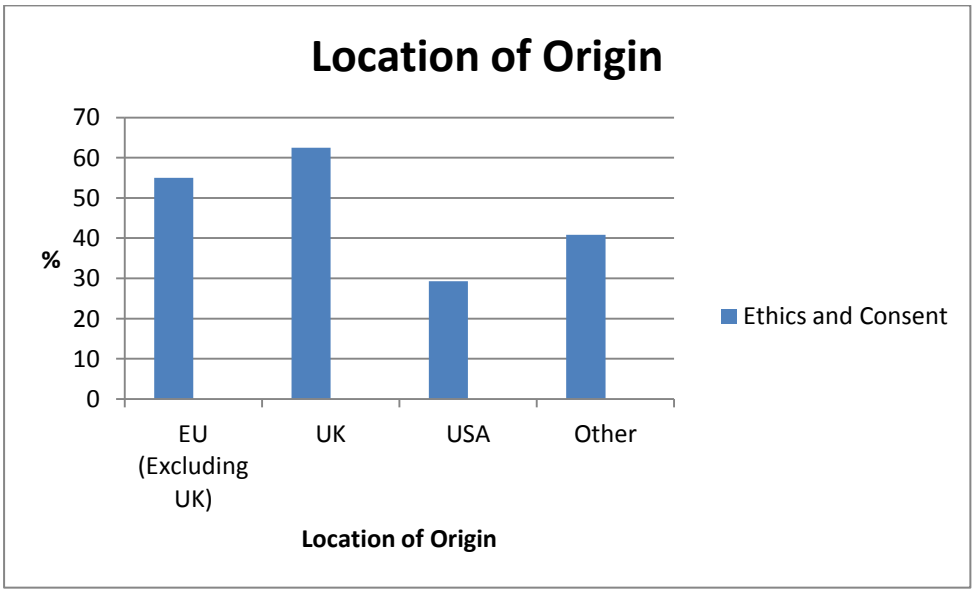


Figure 8. Involvement of a statistician and percentage of RCTs with ethical approval and informed consent or not.

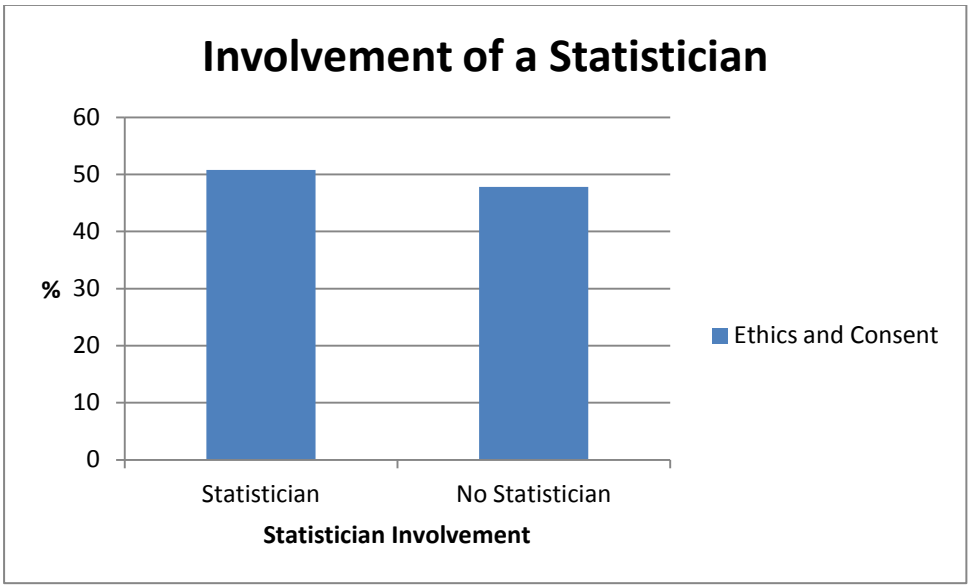


Figure 9. Year of publication and percentage of RCTs with ethical approval and informed consent or not.

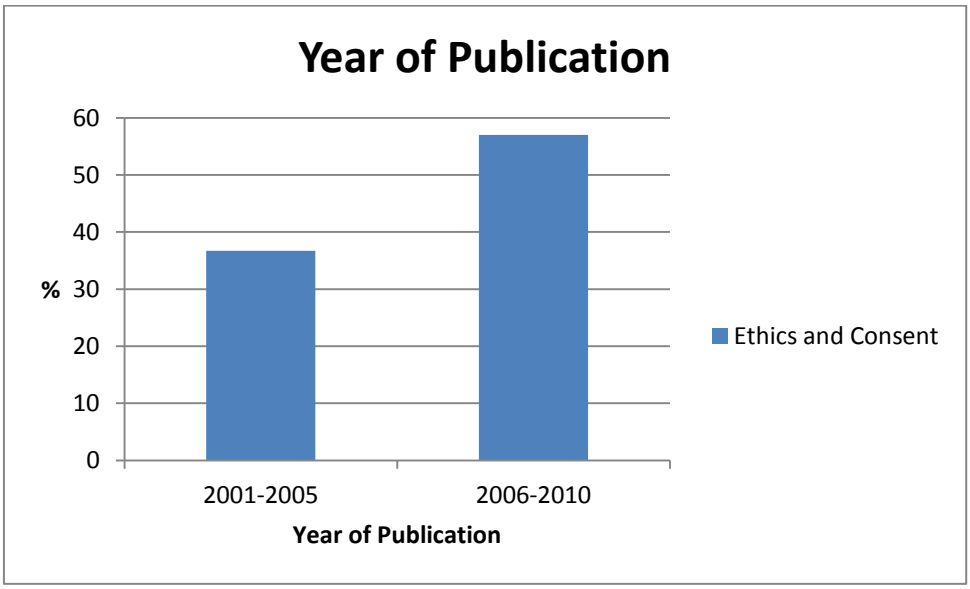


Figure 10. Percentage of RCTs with random* in the title and ethical approval and informed consent or not.

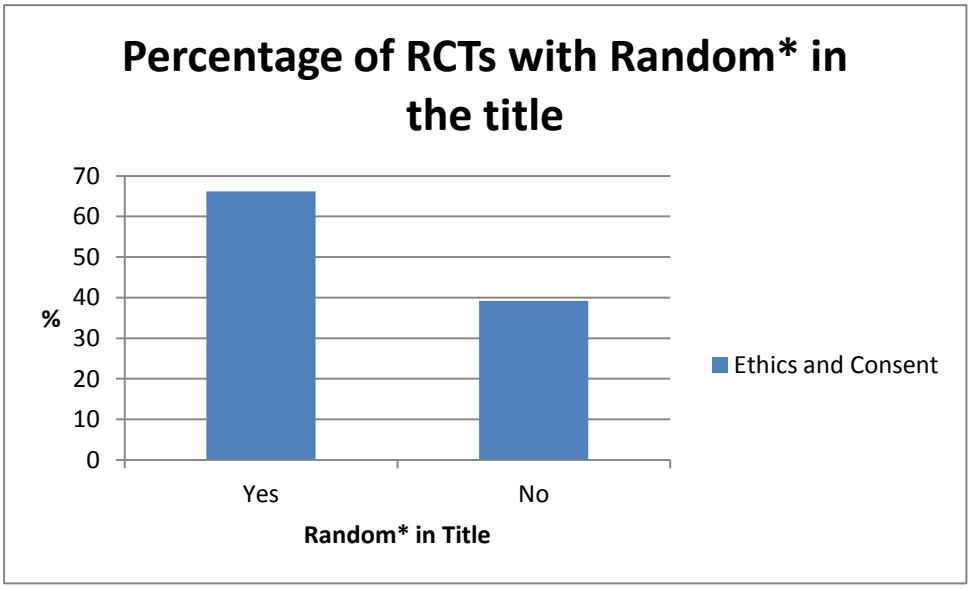


Figure 11. Percentage of RCTs with random in the abstract but not title with ethical approval and informed consent or not.

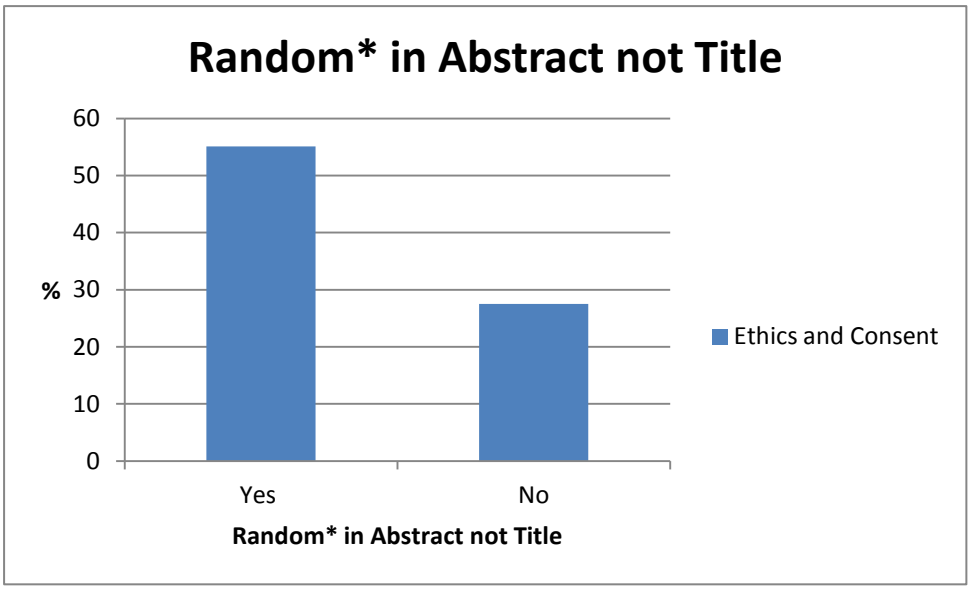
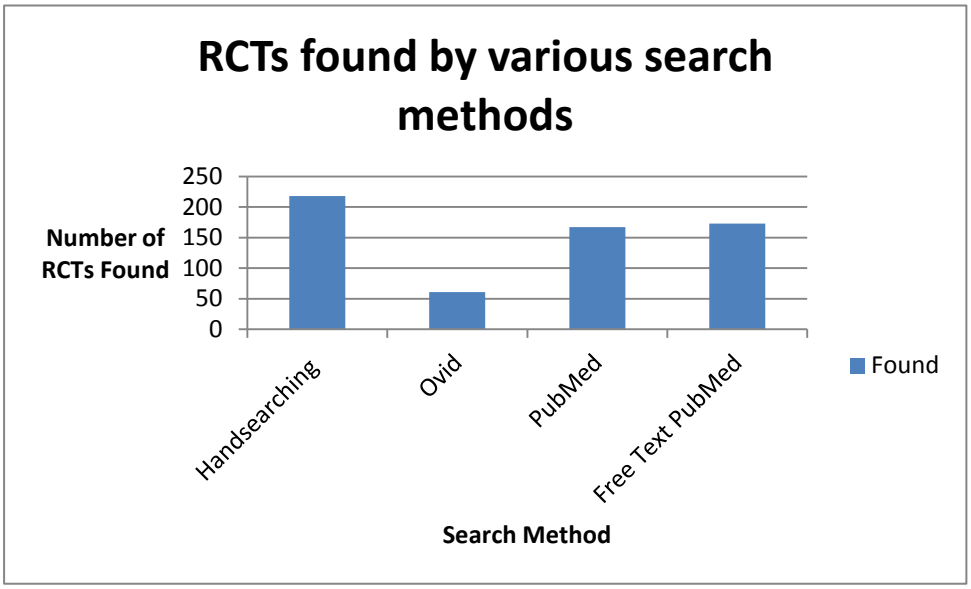


Figure 12. Number of RCTs found and missed by all four search methods.



Appendix 5. Regularity of journal publication

Month	Year									
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Jan	AJODO	AJODO	AJODO	AJODO	AJODO, AO	AJODO, AO	AJODO, AO	AJODO, AO	AJODO, AO	AJODO, AO
Feb	AJODO, AO, EJO	AJODO, AO, EJO	AJODO, AO, EJO	AJODO, AO, EJO	AJODO, EJO	AJODO, EJO	AJODO, EJO	AJODO, EJO	AJODO, EJO	AJODO, EJO, EJO
Mar	AJODO, JO	AJODO, JO	AJODO, JO	AJODO, JO	AJODO, AO, JO	AJODO, AO, JO	AJODO, AO, JO	AJODO, AO, JO	AJODO, AO, JO	AJODO, AO, JO
Apr	AJODO, AO, EJO	AJODO, AO, EJO	AJODO, AO, EJO	AJODO, AO, EJO	AJODO,EJO	AJODO, AJODO, EJO	AJODO, AJODO, EJO, EJO	AJODO, AJODO, EJO	AJODO, AJODO, EJO	AJODO, AJODO, EJO
May	AJODO	AJODO	AJODO	AJODO	AJODO, AO	AJODO, AO	AJODO, AO	AJODO, AO	AJODO, AO	AJODO, AO
June	AJODO, AO, EJO, JO	AJODO, AO, EJO, JO	AJODO, AO, EJO, JO	AJODO, AO, EJO, JO	AJODO, EJO, JO	AJODO, EJO, JO	AJODO, EJO, JO	AJODO, EJO, JO	AJODO, EJO, JO	AJODO, EJO, JO
July	AJODO	AJODO	AJODO	AJODO	AJODO, AO	AJODO, AO	AJODO, AO	AJODO, AO	AJODO, AO	AJODO, AO
Aug	AJODO, AO, EJO	AJODO, AO, EJO	AJODO, AO, EJO	AJODO, AO, EJO	AJODO, EJO	AJODO, EJO	AJODO, EJO	AJODO, EJO	AJODO, EJO	AJODO, EJO
Sept	AJODO, JO	AJODO, JO	AJODO, AO, JO	AJODO, JO	AJODO, AO, JO	AJODO, AO, JO	AJODO, AO, JO	AJODO, AO, JO	AJODO, AO, JO	AJODO, AO, JO

Oct	AJODO, AO, EJO	AJODO, AO, EJO	AJODO, EJO	AJODO, AO, EJO	AJODO, EJO	AJODO, EJO	AJODO, EJO	AJODO, EJO	AJODO, EJO	AJODO, EJO
Nov	AJODO	AJODO	AJODO	AJODO	AJODO, AO	AJODO, AO	AJODO, AO	AJODO, AO	AJODO, AO	AJODO, AO
Dec	AJODO, AO, EJO, JO	AJODO, AO, EJO, JO	AJODO, AO, EJO, JO	AJODO, AO, EJO, JO	AJODO, EJO, JO	AJODO, EJO, JO	AJODO, EJO, JO	AJODO, EJO, JO	AJODO, EJO, JO, JO	AJODO, EJO, JO