

An Introduction to Research for Primary Dental Care Clinicians

Part 4: Stage 6a. Obtaining Ethical Approval

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Introduction

This paper, the fourth in the series, will address the sixth of the ten stages of a research project suggested in the first paper. The ten suggested stages are:

1. The initial idea (asking a research question).
2. Searching the literature.
3. Refining the research question.
4. Planning the study.
5. Writing a protocol.
6. **Obtaining ethical approval** and funding.
7. Piloting the methodology and project management.
8. Collecting data.
9. Analysing the data.
10. Writing up and disseminating the results.

A previous paper¹ has outlined the how to plan a research project. The next stage has two elements, which are to obtain ethical approval and to obtain funding. Each is the topic of a separate paper. This paper outlines the key areas within the topic and updates a previous publication, *Ethical Considerations*.²

Stage 6a. Obtaining Ethical Approval

This paper is divided into the following sections:

- A. Definition of ethics in biomedical research.
- B. The application of ethical principles to clinical dental research.
- C. Research ethics committees.

D. General guidance.

E. Suggested further resources.

A. Definition of ethics in biomedical research

Ethics are rules of conduct. Healthcare teams involved in research are ethically bound to respect human life and people's autonomy. Good research practice demands that researchers:

- Respect the rights of participants in their studies.
- Listen to and share information with them.
- Treat them courteously and caringly.

The rules that apply to research are similar to those that apply to day-to-day clinical practice in that they are a set of principles or a code of behaviour to protect patients from unreasonable actions by clinicians.^{3,4} Over the years, biomedical researchers have agreed to nationally and internationally accepted standards. Clinical dental research is included in the broad term 'biomedical research'. In 1964, the World Medical Association Declaration of Helsinki⁵ underscored 12 basic principles for the conduct of human biomedical research; these have been revised on six occasions, the most recent in 2006.⁶

The issue of research in developing countries was taken up by the Council for the International Organization of Medical Sciences (CIOMS) which, in collaboration with World Health Organization, proposed guidelines for international research. The guidelines were further amended in 1993 as the International Ethical Guidelines for Biomedical Research Involving Human Participants.⁷ A common framework for observational studies in medical research was proposed in 2009.⁸

In the United Kingdom (UK), the Medical Research Council⁹ and the Royal College of Physicians¹⁰ have also published guidance.

A1. Declaration of Helsinki

The Declaration of Helsinki, although primarily designed to protect the health of patients, also mentions the welfare of animals used for research and the protection of the environment. The full version of the Declaration is set out in Appendix C to the booklet Local Research Ethics Committees.¹¹ It offers guidance under three headings:

- Basic principles.
- Clinical research combined with professional care.
- Non-therapeutic biomedical research involving human subjects.

Three overriding objectives are stated:

1. To protect human participants.
2. To conduct research in a way that serves individuals, groups or society as a whole.
3. To examine scientific research activities, looking for their ethical soundness and issues such as risk management, patient confidentiality issues, and informed consent processes.

The key points from the Declaration relating to dental research are that:

- The research must conform to the ethical and scientific principles that justify medical research. It should be based on laboratory and animal experiments or established scientific facts.
- Clinical research can be conducted by doctors, dentists and scientifically qualified personnel under the supervision of suitably qualified personnel.
- Clinical research involving human subjects cannot be legitimately carried out unless the importance of the objective is in proportion to the risk to the subject.
- Every clinical research project should be preceded by a careful assessment of the inherent risks compared to the predictable benefits to the patient.

A2. Clinical research combined with professional care

The principles of clinical research combined with professional care should be understood by all clinical researchers. An investigator can combine clinical research with professional care for the acquisition of new knowledge only to the extent that the clinical research is justified by its potential therapeutic value for the patient.

A3. Non-therapeutic clinical research involving human subjects

In the purely scientific application of clinical research carried out on a human being, it is the duty of the investigator to remain the protector of the life and health of the patient.

- The patient must be given an explanation of the nature, purpose and risks of clinical research.
- Clinical research can only be undertaken after the patient has been fully informed and given free consent.¹²
- The subject must be in a mental, physical and legal position to allow him/her to exercise fully the power of choice.
- Consent should be obtained in writing.
- The investigator must respect the right of each individual to safeguard his/her personal integrity, especially if the subject is in a dependent relationship to the investigator.

- The subject should maintain his/her right to withdraw from the study at any time without penalty.

B. The application of ethical principles to clinical dental research

B1. Aim of clinical research

The aim of clinical research is the generation of new knowledge. This contrasts with the aim of clinical therapy, which is the treatment of a specific patient. However, the distinction is not always clear-cut in that:

- Patients may benefit from participation in a research project by receiving new types of treatment.
- Future patients may benefit from the data collected during clinical research.

A further blurring occurs in that the Declaration of Helsinki requires all patients to be given a detailed explanation of exactly what is involved before they can be enrolled in a research project.⁵ In order to do this, researchers will invariably produce a detailed check-list of points to cover during such an explanation. Thus, it can be argued that potential recruits for clinical research projects may often be better informed and protected than those undergoing routine clinical treatment.

B2. Information to participating patients

When a detailed explanation of what is involved is given to a potential recruit for a research study, the following points should be covered:

- The reasons for conducting the study.
- An explanation of the study design.
- The methods of identification of the participants.
- A list of possible benefits and potential risks.
- The process of obtaining informed consent.
- Privacy and confidentiality.

B3. Reasons for conducting the study

In clinical studies, it is prerequisite that the project is ethically as well as scientifically defensible. In ethical terms, research is justifiable and praiseworthy as long as it causes no significant harm to patients/subjects. Justification must be based on the premise that research is permissible only when it produces beneficial results and limits or prevents harm.

B4. Study design

A further prerequisite of clinical research is that the project is scientifically sound. A scientifically sound project fulfils two ethical requirements:

- It is not wasteful of resources, including funds, patients' time or laboratory space.
- Its design reduces the risk of harm or injury to the patients involved.

It follows from this that no clinical research should proceed without first drawing up a protocol, as described in the previous paper in this series,¹ and having this peer-reviewed by an ethics committee.

B5 Identification and recruitment of participants

Two problems arise from the identification and recruitment of participants:

- Vulnerable patients must be protected from being coerced into a study.
- Denying entry, for any reason, to persons who may benefit from the research.

Participants should be selected for reasons directly related to the problem being studied. It is ethically wrong to select participants because they are easily accessible or can be manipulated or if their position is compromised.

The Hopewood House¹³ and Vipeholm studies¹⁴ carried out before the Declaration of Helsinki are two examples involving unethical dental research. They used vulnerable subjects who were given no alternative but to participate.

People can be vulnerable to the influence that others may have on them or to economic exploitation. They should not be paid to participate in studies but they can be reimbursed for any expenses that they may incur.

B6. Benefits and risks

The research worker must assess benefits and risks at the outset of clinical research. This is part of the justification for conducting the research and must be available and disclosed as part of the informed consent process. The way that it is presented has an important bearing on the perception, interpretation and acceptability of the involved risks.

Ethics committees and peer review groups often lack the expertise to assess risk and benefit. Furthermore, participants and investigators may assess the adverse consequences of clinical research differently.

The conceptual terms 'harm' and 'risk' are ill defined in all relevant codes and guidelines. Risk is the probability and magnitude of future harm. Feinberg (1984)¹⁵ defined harm as psychological, social or economic damage as well as physical damage. Participants may be harmed when their interests have been set back or compromised.

Researchers cannot be expected to identify all threats to the interests of participants but they are expected to make it a duty to identify the likelihood and severity of known risks.

B7. Informed consent

Informed consent is the most important principle in ethical research. It implies that potential participants are given all the relevant information, in a form that they can understand, before they decide whether or not to participate in a study. The process involves an ongoing dialogue between the researcher and the patient to allow the patient full access to all relevant information regarding the project before completing and signing a form. Without informed consent, there must be severe doubts that a patient is being respected, protected from harm, and fairly treated.

Patients can only give informed consent if they have:

- Been given all relevant information in a form that they can understand.
- Been free from any type of coercion or improper inducement.
- The mental capacity to make the decision to participate or not.
- Actively agreed to participate.

The researcher should give the participant a letter or note containing the following points prior to obtaining their written consent:

- The reasons for the study.
- The research techniques to be used.
- The reason why the patient is being invited to participate.
- The benefits and consequences of the study for both the patient and society.
- The anticipated risks, discomfort and inconvenience.
- The time commitment.
- The intent, if any, to conduct a follow-up, study.
- The intent to retain data and what is to be done with the data in the future.
- The extent and manner in which confidentiality is to be maintained.
- Any rules regarding termination of the study and withdrawal of the patient.
- The right of the patient to withdraw from the study without penalty or denial of other treatments.

B8. Privacy and confidentiality

Privacy is a characteristic of limited accessibility to a person. Confidentiality refers to the status of the information about a person and the management of this information. In all clinical research studies, information is gathered that may be termed confidential. In the context of dental research, patients must be protected against undue access to their privacy. Consideration must always be given to their right to be excluded from the study without penalty; in other words, to be left alone.

Patient anonymity can often be maintained by identifying patients solely by numbers rather than by name. However, in dental epidemiological studies, where patient records are used in many instances, restriction of access or confidentiality must always be considered when formulating a protocol.

Each Health Board in Scotland and Trust in England/Wales/Northern Ireland has a Caldicott Guardian(s).¹⁶ The use or transfer of patient-identifiable information, except for normal clinical care, requires approval. Researchers are required to comply with common law confidentiality and the Data Protection Act 1998.

C. Research ethics committees

C1. The aim of ethics committees

The aim of a research ethics committee is to seek to protect the rights, safety, dignity and well-being of participants. In pursuing this aim, it checks that the proposed methodology is appropriate and practical.

C2. Structure and procedures of ethics committees

In Scotland, every Health Board has (or has access to) a research ethics service, run by a scientific officer and comprising several research ethics committees (RECs). There are no longer any local RECs or multi-site RECs (LRECS and MRECs). A favourable ethical opinion is required from only one National Health Service (NHS) REC, even if the research physically takes place at several locations within the UK.

In England, there is the National Research Ethics Service (NRES). Applications for ethical approval are submitted electronically to a local research ethics committee (LREC) chosen by the applicant(s) using the Integrated Research Application System (IRAS) on the NRES website (www.nres.npsa.nhs.uk). This website lists all LRECs in England and details of their chairpersons and secretaries.

Research that does not involve NHS patients or does not take place within NHS organisations may not be considered by NRES or LRECs and may go to university ethics committees for approval. NHS RECs have no remit over research that is undertaken outside the UK, even if it is part of a project approved for the UK.

An REC has up to 18 members with a sufficiently broad range of experience and expertise to reconcile the scientific and clinical aspects of a research proposal with the welfare of patients participating in a study and to assess the broader ethical implications. Members are drawn from both sexes, from a wide range of age groups, and include various medical staff, such as

general practitioners and nurses. At least one third of the membership must consist of lay people. All REC members undergo regular training and all RECs are audited regularly.

RECs discuss proposals at regular meetings. Researchers are always invited to attend the REC meeting at which their application is reviewed and are strongly encouraged to do so. RECs are required to issue an ethical opinion on research within 60 days of receiving a valid application, although the mean turnaround time in Scotland is approximately 30 days. Any substantial changes to an approved study must also be approved by an REC and these will be approved within 35 days. RECs also require the submission of annual progress reports and final study reports.

Broadly speaking, NHS RECs review proposed research involving:

- Patients.
- Their relatives/carers.
- Human tissue.
- Data collection and processing.
- Research on NHS premises.

RECs do not review clinical audits or service evaluations, although the definition of these is a grey area. Further information is available at: www.nres.npsa.nhs.uk/applications/apply/is-your-project-research/

If it is uncertain whether or not a study requires NHS ethical review, it is advisable to contact the local research ethics service for advice. If appropriate, a letter stating that the study does not require NHS ethical review will be provided. This may be requested by editors when submitting results for publication. For details of RECs, see: www.nres.npsa.nhs.uk/contacts/find-your-local-rec/

C3. Research governance in England and Wales

The governance framework in England and Wales is The Research Governance Framework for Social Care¹⁷ and in Scotland it is The Research Governance Framework for Health and Community Care.¹⁸ These frameworks are designed to safeguard patients, researchers and research administrators, and detail standards in five domains:

1. Ethics.
2. Science.
3. Information.
4. Health, safety and employment.
5. Finance and intellectual property.

C4. Non-NHS research

Non-NHS research can be laboratory-based or patient-based. Laboratory-based research involving animals requires the approval of the ethics committee of the institute in which the research is to be conducted before any research is started.

C5. Research and development approval

In addition to research ethics approval, a parallel management approval process is undertaken by the research and development (R&D) department of any Health Board(s) in Scotland and of any Trust(s) in England/Wales involved in the study. Clinical research cannot be started without a favourable opinion from an REC and R&D management approval.

The starting point for this process, the IRAS, is the same for both processes. There is no other way to get NHS research approvals in the UK apart from using IRAS. An online training module on the IRAS website takes you through the process:

<https://www.myresearchproject.org.uk/>

C6. Standards in research

It is accepted that all scientific research should meet agreed international standards.¹⁹ In the UK, all universities and other research institutions have clear policies and protocols for research governance, which require that everyone undertaking research meet standards in a range of areas, including ethics, science, health and safety, and financial probity.

As far as healthcare is concerned, '[c]linical and non-clinical research, research undertaken by NHS or social care staff, using the resources of health and social care organisations and any research undertaken by industry, charities, research councils and universities within the health and social care systems that might have an impact on the quality of those systems'¹⁷ is subject to the provisions in the Research Governance Framework for Health and Social Care.¹⁷

The framework is designed to safeguard patients, researchers and research administrators, and details standards in the five domains listed in section C3 above.

All research-active NHS care organisations (including Primary Care Trusts) are required to have local implementation plans.¹⁷ These are to ensure that any research, funded by or involving the NHS, its patients and its employees (including contractors), is conducted within the Research Governance Framework for Health and Social Care¹⁸ and meets the prescribed standards. Full details of the required standards and the systems for monitoring them are set out in this publication, and also in Research Governance Framework for Health and Social Care—Guidance for Local Implementation Plans.²⁰ These publications, both from the Department of Health, may well be updated from time to time. They can be downloaded from: www.dh.gov.uk/PolicyAndGuidance/ResearchandDevelopment

D. General guidance

The points to consider in any proposal submitted to an REC will depend on the nature of the study in question. Many have been explained in 'Writing a Protocol'.¹ All first-time

applicants are strongly advised to read the booklet Local Research Ethics Committees before submitting a proposal.²¹

Researchers are often critical of the REC process by which their projects are approved, complaining that it is too complex, trying, and sometimes unreasonable. RECs are looking for evidence that researchers are sensitive to ethical issues, in particular to participants' interests, and that information given to potential participants explains the trial fully and truthfully. Researchers can improve their chances of success at ethical review by good preparation and, in particular, by paying attention to the wording of patient information leaflets.

The following subsections give general guidance on issues that frequently result in an unfavourable report by an REC.

D1. Patient care

The care and protection of participants is a key area of concern for RECs. A proposal should demonstrate that:

- Careful consideration has been given to the risks, inconveniences and discomforts to which participants might be exposed.
- Full disclosures of these have been given to participants.
- Measures have been put in place to avoid any risks and to support participants where possible.

D2. Informed consent

Criticism is frequently levelled by RECs at the use of language in the patient information leaflets/letters.

- Use simple language, write in lay terms, and avoid technical terms.
- Ensure that any written material given to participants is intelligible.
- Demonstrate that inappropriate patient expectations have not been created and that trials have not been presented too enthusiastically.

D3. Scientific issues

RECs see scientific issues as having ethical

dimensions. They will look for:

- A design that is scientifically sound (an unclear research question destroys the validity of research and may lead to an unethical study).
- Clearly defined subjects, interventions and outcome measurements.
- A study that has sufficient power to test the hypothesis.

- Subjects that are chosen without bias.
- Exclusion and inclusion criteria that are properly and fully described.

Applicants must recognise the degree to which their proposed research is likely to attract scientific scrutiny from RECs, and prepare

their applications so that the scientific design, rationale, and methods are robustly and clearly explained.

In perusing their remit, RECs check that the proposed methodology, scientific design and conduct of a study are appropriate and practical. They will consider:

- Scientific issues, including flaws in rationale or methods.
- Sampling.*
- The research question.
- Instruments or measures.
- Approach to analysis and power calculation.*

D4. Publishing results

The Declaration of Helsinki expands its guidance to publishing results in Article 16, where it is stated that information regarding any study should be publicly available. Ethical publications extend to publication of the results and consideration of any potential conflict of interest. For these reasons, RECs will expect to receive reports on completion of projects for which they gave ethical approval. Researchers should seek publication only in refereed journals, so that their work is reviewed by their peers before publication. It is scientifically unethical to seek to publish the same report, in slightly different formats, in a number of journals.

D5. Patents and copyrights

Some dental research can lead to the investigators seeking patents or obtaining copyrights. However, it is unethical to use patents or copyright to deny or restrict treatment for patients to limit research.

D6. Fraud

It is extremely unlikely that any dentists undertaking research for the first time would knowingly set out to commit fraud. However, fraud can include the misappropriation or misuse of research funds and the falsification or fabrication of results, which may result in harm to patients from unsafe treatment. Plagiarism of results can also be construed as fraud.

D7. Summary

The key ethical points to consider in oral research projects are:

- Does it have scientific merit?
- Is it justified?
- How will informed consent be obtained?
- Do the benefits outweigh the risks?
- How will the participants be selected?
- How will the privacy and confidentiality of the participants be protected?

E. Suggested further resources

E1. Further reading

- Rhodes R, Francis LP, Silvers A, editors. The Blackwell Guide to Medical Ethics. Oxford: Wiley-Blackwell; 2006.
- Levine RJ. Ethics and Regulation of Clinical Research. New Haven, CT: Yale University Press; 1988.

E2. Useful addresses

The following addresses were current at 12th April 2011. However, the structure of NRES is likely to change in the next 12 months.

England

National Research Ethics Service

National Patient Safety Agency

4-8 Maple Street

London W1T 5HD

Tel: 020 7927 9898

Website: www.nres.npsa.nhs.uk

The NRES also had a series of regional offices at 12th April 2011

Scotland

South East Scotland Research Ethics Service

Waverley Gate

Edinburgh EH1 3EG

Tel: 0131 465 5675

North of Scotland Research Ethics Service

Summerfield House

2 Eday Road

Aberdeen AB15 6RE

Tel: 01224 558480

West of Scotland Research Ethics Service

Tennent Institute

Western Infirmary

Glasgow G11 6NT

Tel: 0141 211 2126

East of Scotland Research Ethics Service

Tayside Academic Health Sciences Centre

Ninewells Hospital & Medical School

Residency Block, Level 3

George Pirie Way

Dundee, DD1 9SY

Tel: 01382 632589

Wales

Research Ethics Committee for Wales

Fourth Floor

Churchill House

Churchill Way

Cardiff CF10 2TW

Tel: 0292037 6829

Northern Ireland

ORECNI

Office Suite 3

9 Haslems Lane

Lisburn

Co. Antrim BT28 1TW

Tel: 028 9260 3107

* These topics will be covered in a later paper in the series.

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