

Practitioners enrolling their patients in clinical research

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SCENARIO

I am a general dental practitioner practising in a small town. I was recently approached by a contract research organisation (CRO) to participate in a clinical trial of a new dental restorative material. I was offered a sum of money for each patient I enrolled in the trial. I was assured by the representative that the trial has received the necessary approvals, including one from an Ethics Review committee. I have never participated in a clinical research trial before and am happy to receive the extra money. I joined the trial immediately, but am concerned now that I did not enquire further about the scientific or ethical aspects of the study. Should I withdraw from the trial?

COMMENTARY

Dental materials and pharmaceutical products are required to have proven evidence of their safety and efficacy before governmental approval may be granted for their distribution and use. In the interest of the advancement of Dental Material Science towards the development of safe, efficacious and innovative treatment, scientifically valid and ethical research of high quality must be conducted. In the past few decades, great progress has been made in the development of new dental materials, devices and techniques and there is more dental research being carried out than ever before. The dental profession has a responsibility to be familiar with the guidelines and legislation related to research ethics.

Research ethics involves the systematic analysis of ethical and legal questions to ensure that study participants are protected, and ultimately, that clinical research is conducted in a way that serves the needs of such participants and of society as a whole. Evidence-based decision making by dentists means that they are utilising the results of dental research in their clinical practice. It is a requirement of the Health Professions Council of South Africa (HPCSA) that all dentists must maintain their competence, and keep abreast with the current research in their area of practice through Continuing Professional Development, reading dentistry journals and interacting with knowledgeable colleagues. This ensures that even if dentists do not engage in research

ACRONYMS

CRO:	Contract Research Organisation
GCP:	Good Clinical Practice
REC:	Research Ethics Committee
UNAIDS:	The joint United Nations Programme on HIV and AIDS

themselves, they are nevertheless familiar with basic research methodology and are able to interpret the results of research and apply them in their daily practice. It is also a requirement of the HPCSA that there is incorporation of research and ethics (including research ethics) components, together with consideration of human rights in the curriculum for both undergraduate and postgraduate programmes at all levels of health sciences education.

A clinical trial is one of the most common methods of research for comparing and evaluating new materials and drugs. Clinical trials have contributed significantly to the knowledge base in dentistry and it is imperative that all such trials are conducted according to the principles of good clinical practice (GCP). The process usually begins with laboratory studies followed by testing on animals. If these prove promising, four phases of clinical research need to take place¹:

- Phase One research, conducted on a small number of healthy volunteers, who are often paid for their participation, is intended to determine what dosage of a drug is required to produce a response in the human body, how the body processes the drug, and whether the drug produces toxic or harmful effects.
- Phase Two research is conducted on a group of patients who have the disease that the drug is intended to treat. Its goals are to determine whether the drug produces any beneficial effect on the disease and whether there are any harmful side effects.
- Phase Three research is the clinical trial, in which the drug is administered to a large number of patients and compared with another drug, if there is one for the condition in question and/or to a placebo. Ideally, such trials are 'double-blinded' i.e. neither research subjects nor their dentists know who is receiving which drug or placebo.
- Phase Four research takes place after the drug is licensed and marketed. For the first few years, a new drug is monitored for side effects.

Due to the rapid increase in recent years in the number of on-going trials, more and more patients are needed to meet the statistical requirements of the trials and many dentists

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are being approached to enrol their patients as research subjects into the trial. However, a dentist needs to consider this request carefully as there may be a conflict between the dentist as a clinician and the dentist as a researcher. It is important to distinguish between the dentist-patient relationship in the clinical setting and the investigator-participant relationship in research endeavours. Traditionally, the dentist-patient relationship is based on concern for individual patients and the patient is seen as the ultimate purpose and beneficiary. In research, the study participant may stand to benefit to a certain degree but the benefit to science and society may be significant enough to render the research participant a means to an end. Therefore the research participant requires special protection of his/her rights in such settings and the dentists needs to be aware of potential conflicts.²

So what makes clinical research ethical? The following concepts, adapted from Emanuel *et al.*³ have been described as the benchmarks of ethical research:

What makes clinical research ethical?

Relevance, scientific, clinical and social value
 Scientific validity
 Fair subject selection
 Risk-benefit ratio
 Independent review
 Informed consent
 Respect for participants

Relevance, scientific, clinical and social value

A research project should contribute to the well-being of society in general and should expand scientific knowledge leading to an improvement in the overall health of the community. Research that lacks social or scientific value is unethical as it results in a waste of limited resources and exploits human subjects by exposing them to potential harm. As resources available for research in health diminish so the issue of social value has become more important. The research objectives, for both scientific and social value, should outweigh the risks and burdens to research participants. The populations in which the research is carried out should benefit from the results of the research. This is especially important in countries where there is potential for unfair treatment of research participants who undergo the risks and discomfort of research for drugs and materials that are going to benefit only patients elsewhere.¹

Scientific validity

Research involving human subjects must be justifiable on scientific grounds and must be conducted in a methodologically sound and rigorous manner. This requirement entails that research protocols must ensure that the:

- aims and objectives are clear and scientific;
- study design is relevant and uses accepted principles;
- sample size has sufficient power to definitively test the objectives;
- methods are valid, reliable and practically feasible;
- data analysis is clear and plausible.

The ethical justification of scientific validity relies on the same principles that apply to the avoidance of exploitation. If patients are being asked to participate in a research project, even where risk of harm is minimal, there should be an expectation that important scientific knowledge will be the result.

Subject selection: must be fair and free from exploitation of vulnerable groups

Research participants should be selected so as to minimise risks and to enhance benefits to them and to society as a whole. Decisions regarding recruitment, enrollment, inclusion into, and exclusion from, the study need to be fairly done according to stated scientific aims and objectives and not according to vulnerability, privilege or other unrelated purposes. In addition, participating individuals or groups who bear the risks and burdens of the research should be in a position to enjoy its benefits. The following groups of people are regarded as vulnerable research participants - children and adolescents, elderly, pregnant women, prisoners, people with mental disabilities, those with substance abuse disorders and 'vulnerable communities'. The UNAIDS has defined vulnerable communities as those with: limited economic development, limited health care and treatment options, limited ability to provide individual informed consent, inadequate HR protection and discrimination based on health status and inadequate understanding of scientific research.

Risk-benefit ratio

A researcher must be able to demonstrate that the risks to the research participants are not unreasonable or disproportionate to the expected benefits of the research. A risk is the potential for an adverse outcome (harm) to occur and has two components (i) the likelihood of the occurrence of harm (ranging from highly unlikely to very likely), and (ii) the severity of the harm (ranging from trivial to permanent severe disability or death). Researchers are required to adequately assess the risks and be sure that they can be managed. If the risk is entirely unknown, then the researcher should not proceed with the project until some reliable data are available, for example, from laboratory studies or experiments on animals,¹ as detailed above in the recommended sequence of trials.

The requirement for a favourable risk-benefit ratio is based on the ethical principles of non-maleficence and beneficence. Non-maleficence states that one ought not to inflict harm and this justifies the need to reduce risks associated with research. Beneficence refers to acting for the benefit of others and this translates into the need to enhance the potential benefits of research to the both the study participant and to society as a whole.³ In many cases, clinical research involves drugs, devices and procedures about which there is limited knowledge. As such there is inherent uncertainty about the degree of risks and benefits associated with these experimental interventions. In any research endeavour the net expected benefit to patients must outweigh anticipated risks. Clinical research can be justified only if the:

- potential risks to the individual participants are minimised;
- potential benefits to the individual participant are enhanced;
- potential benefits to the individual participants and society are proportionate to or outweigh the risks.

Independent review

Conflict of interest may be defined as a "set of conditions in which professional judgement concerning primary interest (eg. validity of research) tends to be unduly influenced by a secondary interest (eg. financial gain)".⁴ In clinical research, there are various levels where there may be a conflict of interest for example in the actions of pharmaceutical industries and their relation to health professionals. Among researchers there may be conflicts related to financial gain associ-

ated with participation in sponsored pharmaceutical trials. Independent review helps to minimise the potential of such conflicts of interest and safeguards social accountability. In some instances, it is difficult to say when a risk is justified in view of the possible benefits related to the research. In many cases participants may not always be able to fully appreciate the risks associated with scientific research and tend to agree with whatever the health professional suggests. The researcher therefore has an obligation to exercise some responsibility over the risks to which participants are allowed to expose themselves.²

In South Africa, all research proposals on human subjects must be reviewed and approved by an independent Research Ethics Committee (REC) before the project, whether clinical trials or primary research, can proceed. In order to obtain approval, researchers must include the purpose and methodology of the proposed research; demonstrate how research subjects will be recruited, how their consent will be obtained and how their privacy will be protected; specify how the project is being funded and disclose any potential conflicts of interest on the part of the researchers. Thereafter the Ethics Committee may approve the project as presented, require changes before it can start, or refuse approval altogether.

In addition, if a drug or device is involved, approval from the Medicines Control Council (MCC) is required in South Africa.

Informed consent

The first principle of the Nuremberg Code⁵ reads as follows: "The voluntary consent of the human subject is absolutely essential" and requires, among other things, that the research subject "should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him/her to make an understanding and enlightened decision". Furthermore, research subjects should be informed that they are free to withdraw their consent to participate at any time, even after the project has begun, without any sort of reprisal from the researcher or dentist and without any compromise of their management and care.

Individuals participating in clinical research must be able to make a voluntary and uncoerced decision regarding participation. In the research setting, obtaining informed consent is comprehensive and includes full disclosure/declaration of all anticipated risks including death. Therefore, to enable valid informed consent, research participants must be accurately informed of the purpose, methods, risks, benefits and alternatives to the research and they must understand the information provided in order to make an informed decision about participation. In South Africa written consent is required in all research projects and, despite the many challenges that arise during the consent process, free, voluntary, valid, informed consent requires special consideration in oral health research.

Respect for participants

Respecting potential and enrolled participants includes:

- respect of privacy by maintaining confidentiality: unlike clinical care, however, research requires the disclosure of personal health information to others, including the wider scientific community and sometimes the general public. In order to protect privacy, researchers must ensure that they obtain the informed consent of research subjects to use their personal health information for

research purposes, which requires that the subjects are told in advance about the uses to which their information is going to be put. As a general rule, the information should be de-identified and should be stored and transmitted securely to ensure anonymity;¹

- allowing participants to withdraw from the study without penalty;
- providing any new information (positive or negative) that becomes available during the course of the study;
- carefully monitoring the participants throughout the duration of the study;
- informing them about the outcomes of the research.

CONCLUDING REMARKS

As can be seen by the commentary above regarding some of the benchmarks of good ethical research, the practitioner in the depicted scenario should have considered all these aspects before accepting the offer to participate. More information regarding the project was required to ensure that it met all the requirements of carrying out ethical research. Written confirmation should have been requested showing that the protocol had been submitted to a REC and was approved without any comment or conditions on the study. While patient autonomy, informed consent, confidentiality, protection of privacy, professional competence, standards of care and rational, sound, scientific evidence are critical components in distinguishing between acceptable and unacceptable research, the determination is ultimately an ethical one and comes down to preparedness, clarity, transparency and respect for human rights and justice.

Before participating in any research one should be satisfied with the scientific merit and social value of the research. If the dentist agrees to participate, then he/she should ensure that the risks, benefits and alternatives are clearly explained to the participant (patient) so that free, fully informed consent can be obtained. The principle of discursive ethics that those who are affected by decisions should have a voice in the decisions means that the profession generally and society as a whole must also decide where the boundaries of acceptable research practice lie. Dentist-researchers should act in the best interest of the patient and only enrol those who will not be harmed in any way. Research participants should be carefully monitored for unexpected adverse events and corrective action should be available if need be. Findings of the study should be communicated to the participants timeously. Knowledge of relevant laws and regulations, the maintenance of personal and professional integrity and detailed execution of the research proposal is essential to ensure that the research aims and objectives are reached.

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