The Ethics of Research: Part 4: Safeguarding the Scientist, Protecting the Participants.

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INTRODUCTION

Traditionally, medicine has been governed by the principle of *Primum non nocere* - "first do no harm", which implies both doing good and avoiding doing harm. However, in medical research, this approach is far too simplistic. Today we need also to be attuned to the vast domain of related ethical issues. In ethics, as indeed in English, many terms and concepts are clearly confusing. They may seem similar, yet be different: is petrol flammable, or inflammable? Others question logic, dishonest and honest, so why not diseased and eased (instead of healthy)? Many terms are also highly debatable; if someone sets out to fail and actually succeeds, is that a success or a failure? This paper will explore some basic principles of medical ethics and then relate them to scientific research in terms of study design. These principles give guidance for the protection and safeguarding of researchers, participants (specifically dental patients), and the community.

PRINCIPLES OF MEDICAL ETHICS

Beauchamps and Childess[1] considered medical ethics in terms of patient treatment under four headings:

- Autonomy or "self-rule", in which patients are empowered to make their own decisions regarding their treatment. However, before they can do this, the clinician is obliged to provide to them assurances of confidentiality, education, understandable communication, truthful details, before finally gaining their voluntary consent.
- Beneficence implies that all interventions should aim to improve health by following accepted standards, with an expectation of success. The intention behind treating must be to always do good, and be in the best interest of the patient.
- Non-maleficence is more than just the avoidance of inflicting any physical, psychological, emotional or other form of pain, suffering or harm. It also refers to taking positive steps to prevent harm or to removing potentially harmful influences.
- Justice refers to fairness and fair treatment. This involves legally respecting morally acceptable laws, fair distribution of limited resources, fair selection of study participants, fair distribution of risks and benefits, and respect for personal rights.[1]

In medical research, these underlying principles apply, and one would assume that by following them, the study would be ethical. However, in reality it is not quite as simple. There are many "non-obvious" scientific areas that have associated ethical aspects. Thus a researcher oblivious to the nuances could inadvertently conduct unethical research, and unintentionally mislead others.

ETHICS OF RESEARCH

It is no longer morally acceptable to justify treatment decisions in the practice of Dentistry with statements such as "in my hands" or "this is what I have always done, so why change?" Today, all clinical practice must be based on "The Best Available Evidence". This has led to an explosion of research into all aspects of Dentistry. However, not all research is sound, and not all results are valid. Investigations are futile unless they are scientifically valid, ethically responsible, the results are subjected to critical appraisal and peer review, and the findings made known publically. Thus evidence based dentistry (EBD) strives to keep clinicians up to date by providing them with educated recommendations that can guide their clinical decision making.[2]

Ethics of study design

Research is defined as "Systematic investigation, development, testing and evaluation, designed to contribute to generalizable knowledge".[3,4]

A valid research project should fulfil two key criteria: it must involve a systematic investigation; and the design and purpose of the investigation should aim to develop or contribute to generalizable knowledge.[4] In addition, all research should be conducted in a scholarly manner with the researcher taking responsibility for the design, methodology and execution of the study. It should be planned in such a way that the findings will be valid, reliable and repeatable. All results (both positive and negative), as well as limitations should be documented and subject to peer

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review, and then made publically available. In both the execution of the project and the communication of the findings the researcher must adhere to the principles of honesty, clarity, comprehensiveness, accountability, and be open to public scrutiny. These principles also apply to the relationships with the research community, research participants, general society and research sponsors. In addition researchers should not misuse their positions for personal gains.[5]

What constitutes unethical study design?

- Poor planning. A design that has not been well thought out and structured is destined to encounter complications. These could delay or even halt the entire study. This results in wasted time (for the researcher and anyone else involved), wasted resources which could have been put to a better use, inconvenience, and depriving society of potential new knowledge.
- Research for the sake of research. Unless there is a specific problem or uncertainty that needs to be answered, it is a futile waste to embark on a meaningless study. For this reason the first steps in any study should be to identify a question and then to conduct a thorough literature search to make sure that the answers are not already known.[3]
- Having a pre-meditated assumption or wish as to what results will be obtained. This can tend to bias the manner in which the entire study is performed and will certainly prejudice analysis and interpretation of the results.
- Poor science. Inexperience, lack of background knowledge and expertise, unstructured design, non-adherence to recommended protocols, not following manufacturer's instructions, and faulty techniques, all constitute poor science. By association this equates to unethical research as the results will be unreliable, invalid and unrepeatable. A worse scenario is that others may accept the results as true and use the study as a basis for their actions. If patients are involved the outcome could be dire.
- Not having statistical knowledge, and then failing to consult a statistician. It is imperative that the type of study design is clearly described before planning the methods. A statistician will be able to advise on which tests could be used to answer the research question, and will then be able to calculate the minimal sample number needed for this application. Guidance may also be provided on sampling methods, randomization, blinding, coding to allow for anonymity, and prevention of selection bias.
- Failure to consult and take advice from experts in areas beyond the expertise of the researcher. Once again, this is unethical as it may jeopardise the quality of the study and potentially limit the strength of the findings. It should be borne in mind, however, that in any collaborative study, it is imperative to agree upfront on the partnership roles, amount of input and benefits in terms of authorship and publications.
- Non-adherence to manufacturer's instructions for material use. As mentioned above, this could lead to unreliable and invalid results, which may not be repeatable by others. If published, others may use this erroneous information to the detriment of their practice and their patient's health.
- Non-adherence to the documented protocol. Changing methods mid-way (unless a patient's life is at risk, or any serious adverse events have been noted), could alter the entire study, and lessen the validity and reliability of the results. If changes are needed, the reasons for, and the time and nature of, the deviation, should be documented and declared in the final write up.
- Any form of dishonesty or research fraud. Altering data, omitting negative results, plagiarism, even unintentional misrepresentation due to sloppy work and inaccurate results all constitute fraud as they deceive others into believing false information.
- Plagiarism. Copying other people's ideas, duplicating studies or quoting literature without acknowledging the original pioneer constitutes plagiarism and is considered research fraud.[6]
- Accepting remuneration from companies to conduct research. Sponsorship of materials is common in clinical trials. However, accepting remuneration in exchange for conducting studies for private companies can jeopardise the integrity of the research. This is particularly so in situations where the sponsors interfere, or retain the results. There is the risk that negative findings may then be concealed. To safeguard the researcher, the nature and amount of sponsorship and remuneration must be declared, and a statement issued to the effect that there is no conflict of interest. Details of all donations and remuneration for both the researcher and the study participants should be outlined in a written contract. This should also state that "all findings will be made responsibly and freely available to the public within a specified, limited timeframe".[5]
- Failing to complete a research study. Poor planning, insufficient funds, lack of time, poor judgement, inexperience, lack of required skills, loss of interest, or any other preventable obstacle that leads to the study being aborted is unethical. This results in wasted time, reduced resources, inconvenience, and denies the broader community of new knowledge.

What constitutes unethical participant recruitment, selection and management?

Clinical trials need to be conducted in accordance with the ethical principles laid out in the Declaration of Helsinki. Accordingly, the rights, safety and well-being of participants must always be the primary concern, and should prevail over the interest of science or society.[6] Any research involving study participants, especially if they are also patients, carries a risk of their being vulnerable or exploited. This may be due to power differentials, economical disadvantages, pain or medical debilitation, and language or education barriers. It is particularly relevant in developing countries where patients may rely on the presence of a research project to make goods, services and treatment available to them.[7] The Council for International Organizations and Medical Sciences (CIOMS) has set guidelines on the ethics of clinical trials in order to protect vulnerable populations.

They state that informed or valid consent must address three questions: 1) does the patient have the capacity to consent (age, maturity, cognitive ability); 2) is the consent voluntary and 3) has the patient received sufficient information on which to base their decision?[8]

It is important to note that consent is a process and not an event. Patients need time to think before agreeing, and must be able to withdraw at a later stage for any reason without question or repercussions.

- Unfair or unequal selection of sample and control participants. This could skew the results and also advantage / disadvantage certain people at the expense of others. It occurs when there is selection bias or a lack of random selection and blinding.[3,9]

- Preferential benefits by virtue of being in the study group. In any situations where an intervention, treatment or therapy is being tested, the control group must be given the gold standard if it exists. A placebo is only ever warranted where there is no accepted standard of care, and the participant is fully aware that they may or may not be in the experimental group. In addition, if the results of the study are positive, the control should also be offered the treatment, device, or new discovery for free.
- Research carried out on a population group who will not benefit after conclusion of the study. "Those that bear the burden of research ought to receive the benefits".[10] Subjects selected should not have a history of acquiescence, neither should they be excluded from the benefits of the research if it is proven successful. This includes provision of therapy for those who were allocated to the control group.[10] In addition, there should be some foreseeable advantage for the community to which the study participant belongs. Socially responsible investigators should make provision for benefits to be allocated to the broader society, albeit for a limited period of time.
- Non-therapeutic research. Ideally the research and interventions should also be therapeutic in nature, or if non-therapeutic, should pose minimal risk.[8] However, in the case of non-therapeutic surveys, the observers are morally bound to provide referrals, follow up treatment and feedback to study participants (if they have indicated that they would like this, in which case anonymity becomes an ethical issue).
- Not maintaining confidence. Almost all studies involving human participants are anonymous and results are confidential. The only time this may be overturned is when findings could put a third person or the wider community at risk.
- Provision of a device (specifically dental implants) for research purposes, without making provision for the follow up treatment (superstructure) or maintenance. Manufacturers have been responsible for a universal explosion of research into new implant systems. Many uninformed patients benefit from "free" implant placement, but are not warned of the additional costs that they will have to incur in placing restorations and in subsequent maintainance. This has led to an unacceptably large pool of patients with buried or non-functional implants, who have not reaped any benefits for the burden of their participation. There should always be a written agreement as to the extent of the investigator's involvement and responsibilities both during and after the trial, as well as a time limit for these.
- Coercion, giving false promises or creating unrealistic expectations. This includes offering remuneration or other incentives, in order to recruit study participants. It invokes people's vulnerabilities (economic, physical, educational, social) and may entice them into taking increased risks that the "average man" would not take under normal circumstances.
- Promising treatment (or denial of same) in exchange for participation in the study. As above this is a form of coercion that preys on the vulnerabilities of participants.[8]
- Not communicating with study participants. The researcher must ensure participants are educated and informed about all aspects of the study. This includes giving all the relevant information both verbally and in a written form, in the appropriate language and style, taking into account cultural differences and sensitivities. Consent is a process, not an event, and recruits should be given time to think and consult with others before giving free and voluntary consent. They should also be made aware that there will be no penalties or withholding of treatment should they decline to participate, and that they are free to withdraw at any time during the course of the investigation.[8] Note, this does not refer to situations where data has been gathered or questionnaires have already been answered and submitted. These cannot be later retracted.
- Lack of equipoise. This concept is best explained as a consideration of the balance between the risks of the experiment and the beneficial outcomes.[10] Studies with minimal risk to the subject and high benefit to the scientific/patient community pose no problems. However, those with increased risks to the participant and small benefits for society are considered unethical, and should not be undertaken.[3,10]
- Not being culturally aware or sensitive. Certain interventions may not be culturally acceptable in a wider community. Exposing study participants to such activities may render them subject to repercussions when they return to their communities.

CONCLUSIONS

Researchers and specifically clinician-investigators, should always be cognisant of the relationship and power differentials that exist between themselves and their patients and /or study participants. Patients seek help to address issues that concern them, while study participants help the researcher address issues that concern him/her. Many times the two may overlap where the provision of treatment is also the subject of the investigation. In general, any research involving human subjects should be submitted to a relevant ethical review board for approval. Their approval helps safeguard researchers, as well as provides protection of the study participants. A final ethical question to consider is when is treatment routine, and when does it become "experimentation"? (This will form the basis of Part 5 in this series). In conclusion, any person carrying out scientific research has an ethical and moral obligation to conduct themselves professionally, and to place the interest of patients, the scientific community and the general public above personal goals and desires.

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