Ethical Issues in Translational Research: From the Bench to Theatre

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Surgical research has resulted in the continued use of some procedures whose efficacy is questionable (1). This has led to a perception that surgical procedures do not undergo rigorous ethical and methodological scrutiny as compared to medical treatments; and this has resulted in procedures being "smuggled" into practice without appropriate review (1). This is one of several scientific and ethical issues that arise in the translation from basic science to research on human participants; a field of research referred to as translational research/translational medicine. The American Physiological Society defines translational research as "The transfer of knowledge gained from basic research to new and improved methods of preventing, diagnosing, or treating disease, as well as the transfer of clinical insights into hypotheses that can be tested and validated in the basic research laboratory"(2). Translational research aims for a smooth transition of discoveries made through laboratory based basic research to their clinical application. These applications may influence current clinical practice and health policies (3). This translation from the "bench to the bed side" is a lengthy, laborious, resource intensive process that requires effective national and international collaboration, and efficient coordination between key stakeholders (4).

Translational research involves first in human trials where experimental products and techniques get tested on human being for the very first time (5). These clinical applications include but are not limited to novel pharmaceuticals, medical devices, biologics surgical procedures (6), gene transfers (5), cell therapy (7, 8), nanotechnology (4)and regenerative medicine (6, 9). Human trials in several instances are complicated particularly if the experimental products involve novel cutting-edge technologies whose mechanism of action and target are not clearly known, and there is no credible reliability and validity pre-clinical data (10). This makes risk-benefit analysis particularly difficult during the ethical approval process. However, if there is no adequate evidence of benefit to the patient, then the risk level should be no more than minimal risk. To improve ethical and scientific decision making in translational research, there is need for scrutiny of methodological features in pre-clinical studies that address threats to internal, construct and external validity (11).

The transition from "bench to bedside" poses several critical ethical challenges that may be common to all clinical trials but differ both in form and complexity (3). These challenges are more pronounced when it comes to surgical research. To date, there is no clearly delineated method of evaluating novel surgical procedures and ensure adequate oversight of surgical research (12). The is no regulatory agency that evaluates and reviews novel surgical procedures before their widespread translation into practice; and this has raised concerns about "non-validated surgical procedures" being smuggled into practice without undergoing randomized clinical trials (RCT) or review by research ethics committees (REC)(13). While some new surgical procedures involve a totaly new approach to the disease, some just require a change in the sequence in events during the procedure. The study by Bundi et al in the current issue raises the prospect of harvesting less tissue than has been the case previously in patients undergoing ligament reconstruction (14). This potentially has less ethical issues than introducing a totally new procedure.

In most countries the approval process of these novel clinical applications is not clearly defined. In fact, international and local ethical guidelines for research involving human participants do not have specific guidelines for surgical research. For instance in the United states of America, novel surgical procedures are

not regulated by the Food and Drug Administration; they can be applied as and when they are needed at the discretion of the surgeon (6). Problems seem to arise from the blurred distinction between innovative surgical procedures and research. Such lacunae in the regulatory process can be exploited and abused by surgeon-researchers to the detriment of human beings. Locally, RECs are delegated the responsibility of safeguarding the rights, safety and well-being of research participants. Thus, this requires RECs to be cautious and strictly follow regulatory guidelines. However, in doing so, RECs have been perceived as paternalistic and a hindrance to translational research (4). There is therefore urgent need to clearly define the approval pathway of new surgical applications at national and international level.

One of the most controversial issues in surgical research is the use of a sham surgery arm in RCTs. Commentators advocating for sham surgery argue that it is ethically acceptable so long as the risks are minimal, informed consent is obtained from participants, there is clinical equipoise and there is no suitable methodological options to use in the control arm of the trial (15, 16). On the other hand, opponents of sham surgery in RCTs see no reason in subjecting patients to surgery that has no benefits. They are also wary of therapeutic misconception among participants and the active deception of the patient required when using a sham arm of surgery (1). Therapeutic misconception per se can be avoided through proper informed consent (17). Informed consent should not be a mere bureaucratic formality; participants should be provided with relevant information about the research and given time to assimilate and understand before making a decision whether or not to participate in the research. Therefore, for prospective research, efforts should be made to follow local regulatory guidelines and also ensure informed consent is obtained from all participants before enrolment in the study. Where the surgeon-researcher is in doubt consultations should be made with a local REC. In this issue the paper by Shaban on skin allograft raised some ethical issues that were resolved by consulting the local ethics body (18)

All research and experimentation must be conducted in a way that assures the protection of patient safety and cultivates trust in the research field as a whole. Irrespective of the potential benefits, the quest for generating generalizable knowledge must never come before the safety of patients. This is clearly indicated in Article 8 of the Helsinki Declaration that states: "While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects" (19).

Surgeon-researchers should be wary of conflict of interest especially when there is financial gain. Participant's safety and well-being or the validity of the research tend to be influenced most by conflicting interests (20). To maintain public trust and professional belief in the surgical research enterprise, surgeon-researchers and local RECs should ensure that conflicts of interest do not influence research. Regulators of research should be careful about possible manipulation of research for commercial purposes. This has been termed "translational medicine in reverse" and it involves the conversion of commercial products into scientific concepts without any evidence base (21). Therefore it is imperative that surgeon-researchers uphold high levels of integrity and ethical sensibility but, this should not be a substitute for regulatory oversight (22).

In view of the above challenges in translational research, there is need for paradigm shift to an entirely new concept of clinical research ethics that is more inclined towards clinical research than physician-patient relationships (23). This does not mean that a new set of principles be developed, it is simply a "call for the application of logic to identify the right procedures by applying the basic ethical values of research with human (participants) to the specific context"(3).

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