From Experimental Technique to Clinical Practice: Which Pathway in Transplant Surgery?

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ABSTRACT

The question of whether a medical procedure is to be considered experimental or routine practice has enormous practical implications. In transplant surgery, as compared with pharmacologic clinical trials, the transition from experimental procedure to normal care is far from clear cut. Clinical trials comprise 4 well-established phases of evaluation going from phase I, aimed at assessing safety and identifying side effects in a few healthy volunteers, to phase IV, which involves entire populations and is aimed at long-term postmarketing surveillance. In transplant surgery, technical progress and experimentation follow more atypical and individual routes. As compared with pharmacologic research, the decision about "routine practice readiness" of a surgical procedure does not rely on a standardized formal act but rather on experts' capacity to find a consensus based on best practices and on ad-hoc criteria as well. Independent assessment by a panel of experts and oversight by an institutional review board are key to facilitating meaningful protection of transplant recipients and allowing the research to go forward. The framework of the human subjects protection regulations should also consider the transplant of organs that have previously been part of a research project.

EXPERIMENTAL techniques in transplant surgery do not follow the typical route of randomized clinical trials. Thus, it is necessary to establish the amount of evidence needed to consider a transplantation technique as no longer experimental but rather routine clinical practice. This problem is closely connected to the regulatory framework of new transplantation techniques. Current regulations do not provide operational rules or recommendations on this matter. The question of whether a medical procedure is to be considered as experimental or routine practice, and the criteria to shift from an experimental setting to a routine setting both have enormous ethical, clinical, and regulatory implications. At a different level there is the question of whether someone who receives an organ that was part of a research protocol study should be considered as a study participant in a research study.

In this study we discuss ethical implications at both levels: the shift of a new technique from the experimental to the clinical practice setting, and the experimentation on organs to be transplanted.

NEW TECHNIQUES: FROM EXPERIMENTATION TO CLINICAL PRACTICE

Clinical trials are the mandatory bridge between preclinical discovery of new medicinal products and their general uses. This means that clinical trials must take place before new research treatments can be made available to the public.

Clinical trials follow a rather fixed pattern. In a phase I study, a new research treatment is given to a small number of patients. Researchers must find the best route for administering the new treatment and the "maximum tolerated dose" of it, watching carefully for any harmful side effects. Phase II studies aim to determine the activity of a new treatment and involve about 40–80 patients. Phase III studies aim to compare a new treatment with a standard one to determine which one is more effective. Phase III studies usually involve a larger number (several hundred or thousands) of patients in order to provide significant clinical and statistical data. Phase IV consists of postmarketing surveillance.

The most important design techniques for avoiding bias in clinical trials are randomization and blinding, which represent the "gold standard" of evidence-based medicine

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(EBM). Randomization of trial participants aims to reduce selection bias, which usually results from enrolling "preferred" research participants into one treatment group over another. The term "blinding" refers to keeping trial participants, investigators, or evaluators uninformed of the assigned intervention. Blinding should be maintained throughout the conduct of a trial and, therefore, treatments should remain indistinguishable.

Procedures for conducting randomized clinical trials (RCTs) can generally be applied to any field of medicine, but they are not easily adaptable to surgery. This is due to procedural factors (the double-blind procedure is clearly inapplicable in surgery), and ethical considerations as well (in particular, "sham" surgical procedures or "placebo surgery," would raise serious concerns).

From a purely methodologic viewpoint, sham surgery, could provide surgical experiments with the methodologic rigor applied to RCTs [1]. In sham surgery the patient is anesthetized, the surgeon makes some incisions, and then the incisions are sewn up so that the patient believes the surgery took place. There are indeed those who hold that the use of sham surgery in surgical experiments—in other words, the adoption of procedures similar to those of RCTs—is not only a proper procedure for acquiring scientifically sound knowledge but also ethically acceptable [2]. However, besides deceiving patient, sham surgery clashes seriously with the ethical duty of physicians not to harm the patient, which would be subjected to a real but therapeutically useless surgical intervention [3].

As a consequence, surgical innovations are not based on procedures that have been strictly validated in scientific or biostatistical terms, as in RCTs. New surgical techniques (above all in transplantation) are often not innovations but rather a result of evolution and improvements of existing techniques. Successive adaptations of existing techniques lead to the emergence of new procedures that are not radical innovations produced by a specific research program, but rather part of a *continuum* arising from the evolution of day-to-day practices. More rarely, audacious departures from the norm lead to improvements in existing techniques.

Criteria for a technical and ethical analysis of surgical innovation have been proposed. In particular:

1. In 2000, Moore proposed criteria that include laboratory background, field strength, and institutional stability [4]. Laboratory background requires that any research effort has already been made in several animal species and follows a step-by-step procedure to optimize the intervention and to increase safety before trying the procedure with humans. Field strength requires that adequate synthesis of knowledge and expertise is available from all fields related to the procedure. Institutional stability addresses the overall level of expertise at the institution where the procedure is performed, including the quality of all clinical services, support services, and their capacity to interact in an interdisciplinary manner. Moore did not include mandatory controls or oversights as an ethical obligation for surgical innovation.
2. In 2009, Barkun and coauthors [5] proposed a 5-stage paradigm to describe the development of innovative surgical procedures. Stage 0 and stage 1 (Innovation) are usually the earliest steps in innovation and both relate to the first time a procedure is done: stage 0 is the initial pre-human work and development, whereas stage 1 refers to the first time it is used in humans. At stage 2a (Development), the technical details of the operation and the equipment have improved but the details have not been completely worked out. The technology is deemed by the few surgeons who are carrying it out to probably be safe and can be tested more broadly than before, although it is still experimental. At stage 2b (Early Dispersion and Exploration), individual learning curves are progressing quickly, especially among the original innovators. Indeed, many technical details of the operation have been perfected by this point. At stage 3 (Assessment), the procedure is part of many surgeons' practices and passes the transition point: the innovation is quickly becoming the standard of care, and soon only a few surgeons will not have adopted the new technique. Stage 4 (Long-term Implementation and Monitoring) relates to how the procedure is doing in routine practice, and the perspective is a long-term monitoring.
3. In the same year, McCulloch and coauthors proposed the IDEAL recommendations [6] for the assessment of surgery based on a 5-stage description of the surgical development process, including: (1) Idea; (2a) Development; (2b) Exploration; (3) Assessment; and (4) Long-term Study.

The IDEAL phases partly correspond to the 4 phases of clinical trials, in that their main purposes and outcomes go from the proof-of-concept in stage 1, to the focus on safety in stages 2a and 2b, to a deeper evaluation of clinical outcomes in stage 3, to surveillance and assessment of long-term outcomes in stage 4.

In general, as compared with pharmacologic research, surgery often lacks a centralized, regulatory framework that require studies of efficacy before a new procedure can be offered to patients.

Oversight mechanisms are mostly based on peer review related to the specific discipline rather than on universal methodologic standards for study design.

In Italy, for example, experimental transplantation procedures are regulated by an agreement adopted by the State-Regions-Autonomous Provinces Conference, which states that: "For experimental transplantation procedures, the National Transplant Centre, after having examined the request and the opinion of the Ethics Committee, and having consulted the High Health Council, has the faculty of approving the proposed protocol for a limited number of transplantations. The National Transplant Centre is also in charge of monitoring results of experimental transplants" [7]. The agreement does not provide a definition of

"experimental transplantation procedures." It regulates thoroughly new transplantation, but is enforceable also for new surgical techniques.

Therefore, in Italy, as in other countries, a key role is played by institutions assessing the different implications of the new technique, usually through commissions of experts. This leads to the adoption of mandatory guidelines or regulations.

ORGANS THAT WERE PART OF RESEARCH

Another issue that requires clarification involves establishing whether the recipient of an organ that was part of research involving the donor also needs to be considered as a research subject [8]. In other words, the question is whether organs that have been explanted as part of a research protocol should be equivalent to investigational drugs. Under current regulatory definitions, in most nations, the transplantation of an organ that was explanted as part of a research study is not to be considered as interventional research and recipients are not considered as "research subjects."

This does not obviate:

- The importance of informing transplant recipients and the surgeons of the possible clinical implications of accepting organs that were part of an experiment.
- The need for consent from recipients.
- The importance of getting advice via institutional review board (IRB).

However, in the case of "significant organ manipulations" during the donor intervention research, recipients should be considered as research participants, and many regulatory challenges arise. A definition of "significant manipulations" should be provided by detailed regulation.

CONCLUSIONS

The World Medical Association "considers that, although many transplantation procedures have become standard medical care for a range of medical conditions, others are experimental and/or morally controversial and require further research, safeguards, guidelines, and public debate," and further states that "experimental procedures require protocols, including ethics review, that are different and more rigorous than those for standard medical procedures" [9].

We have to acknowledge that validation methods typical of clinical trials are not applicable to transplant surgery techniques. Moreover, in most cases, randomization and blindness would be unethical: experimentation in transplant surgery is a typical example of "a tension between the highest standard of research design and the highest standard of ethics" [10].

Randomization may be adopted in particular circumstances (eg, transplantation of organs that were part of a research protocol). However, current regulations about clinical trials do not include these techniques. Also, an effort should be made to translate to transplant surgery the capacity to estimate *a priori* the study power and the sample size—as in RCTs—before deciding about routine practice readiness in transplantation.

Of course, it would be more difficult to make estimates on routine readiness for life-enhancing transplants where the primary endpoints are less clear cut than the mortality or life-extension ones.

In the absence of validation methods and regulations, sound scientific methodology and high ethical standards can be guaranteed by:

- Approval and oversight by an IRB, which can facilitate meaningful protection of transplant recipients and allow research to go forward.
- Independent assessment by a panel of experts.
- Appropriate reporting of surgical series results, also through transplant registers.

In most cases, transplant researchers will have to decide which variations from standard procedures should be considered as normal departures from routine practices, always, taking into account individual patient peculiarities. Researchers should also establish which procedures are as sufficiently novel to require an assessment by other experts or undergo an authorization process.

IRBs should be intellectually ready to express opinions—not necessarily binding—on experimental surgical protocols, as very few of them are currently subject to such scrutiny.

Evaluation by an IRB could promote both the scientific soundness and the ethical validity of new techniques, in particular the risk/benefit balance.

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