

From bench to bedside and to health policies (and back): ethics in translational research

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Abstract

Introduction. The medical aim of translational research is to smooth the transition of discoveries made through basic research from the laboratory bench to their diagnostic or therapeutic applications for patients. These applications may be extended to current clinical practice and to health policies.

Aim. The converse is also important: health policies should provide a point of departure when identifying research priorities. Translational research poses the same ethical problems as trials with human subjects – albeit in different ways. One of the more significant problems is the risk for participants in trials: it is thus necessary to ensure that the risks to which these subjects are exposed are not out of proportion to the expected benefits.

Discussion. Translational research does not require new ethical principles, but existing biomedical principles need to be adjusted to the specific context. The well-being of participants should always be the primary objective; these persons should never be considered as means for the advancement of knowledge or for the improvement of applications.

Key words

- bioethics
- clinical trials
- human research
- investigational drugs
- risk
- therapeutic research

FOREWORD

Following its appointment by the Health Ministry, the Istituto Superiore di Sanità (ISS) has contributed, together with the Ministry of Education, University and Research (MIUR) to the planning and creation of three key research infrastructures for health in Europe. One of these is the European Advanced Translational Research Infrastructure (EATRIS).

The present article is the result of the author's cooperation in: 1) the planning stage prior to the establishment of EATRIS; and 2) the "front door", for ethical issues, of the Italian Advanced Translational Research Infrastructure (IATRIS), the Italian arm of EATRIS: the text is based on a conference given by the author to the Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST).

WHAT IS TRANSLATIONAL RESEARCH?

Wolfgang Goethe was certainly not thinking of translational research when he wrote: "Knowing is not enough; we must apply. Willing is not enough; we must do". His words nonetheless neatly encapsulate the essence of translational research: the transition from knowledge to its application.

Knowledge translation

The notion of "translation" can be applied not only to the field of biomedical research, but to a number of

other fields of knowledge, and there are many ways of describing it: "Many terms are used to describe the process of putting knowledge into action" [1], one particularly effective one being "knowledge translation" [2].

The Canadian Institute of Health Research (CIHR) is one of the institutions that has examined knowledge translation in depth. The CIHR researchers have defined it as "A dynamic and iterative process that includes synthesis, dissemination, exchange and ethically sound application of knowledge to improve health (...), provide more effective health services and products and strengthen the health care system" [3].

The present article refers to "translational research" in the biomedical setting.

The American Physiological Society has adopted a much-quoted definition of translational research: "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" [4].

The issue is of primary significance: in recent years "the United States, Europe and Japan have seen sharp rises in the attrition of drugs tested in trials" [5] and "Most of the product failures in phase II and III trials are because researchers are unable to demonstrate efficacy or sufficient safety". The Food and Drug Administration (FDA) described the problem as a "technolog-

cal disconnection between discovery and the product development process" [6].

From bench to bedside. From bedside to clinical practice and public health

A catch phrase that is much used to indicate translational research, particularly in less strictly scientific contexts, is "From bench to bedside". The translational researcher has been described as "someone who takes something from basic research to a patient and measures an endpoint in a patient" [7].

The steps along this path have been variously classified. Woolf, for instance, identifies T1 as the phase in which new knowledge relating to the mechanisms of disease gathered in the laboratory is transformed into the development of new procedures for diagnosis, therapy and prevention, and includes their initial trials in humans; T2 is the phase in which the results of those clinical trials are translated into everyday clinical practice and taken into account when health decisions are made [8].

Fiscella and co-authors propose additional subdivisions: they suggest that preclinical research should be divided into: long-term preclinical translational research, of 5-10 years, and short-term preclinical translational research, of less than 5 years. For applied clinical research (ACR) they propose a subdivision into: clinical ACR, patient ACR, organisational ACR and community-focused ACR [9].

Translational research can thus be transferred not only "from bench to bedside", but also from the bedside to clinical practice, to general policies and, finally, to public health. Public health policies should be based, among other things, on evidence generated by clinical practice: "Public health is *de facto* a translational industry that concerns itself with bringing about improvements to the health of populations through the best science" [10].

POSSIBLE STRATEGIES TO PROMOTE TRANSLATIONAL RESEARCH

Concerted action by several disciplines

Although the objective of translational research is to reduce the interval between a scientific discovery and its application, the process is not brief and it involves numerous areas of competence.

According to Abani and Parakken, "structures that are needed to move an idea from its conceptual stage to early clinical development" are: "intellectual property, scientific advances, early clinical development, licensing to industry spin-off, financial returns, funding for investment pools" [11]. These authors also believe that "key areas that a researcher must traverse in the translational medicine itinerary and in which support structures might be developed to improve the chances of success" are: "basic science department, innovative technology, lead identification development, knowledge of human disease, access to patient, clinical science department, preclinical development" [11]. More particularly, these authors identify the areas of "biomedical research, intellectual property, funding, regulatory agencies, legal issues, ethical issues, communication skills, preclinical testing, design of preclinical and clinical trials" as those

in which fundamental "tools and skills" are needed [11].

It is clear from these lists that a multitude of dissimilar skills and competences are needed to accompany the transition from bench to bedside and that translational research is a complex and multidisciplinary affair.

In reverse: from practice to research

While encouraging the transition from research to clinical practice, we should not forget the importance of the reverse route from clinical practice to research. Walley and co-authors noted that "The current model for most international health service research is based on the assumption that the research community "discovers" solutions and then tries to market them to busy decision-makers and practitioners" [12] and stated that this approach is "necessary but not sufficient. The aim should not be to perfect techniques of feeding results to decision-makers, but to start from the perspective of the decision-makers even before devising the question. This means "getting practice into research" [12]. They added that "This approach is not appropriate for research into new and untried treatments where efficacy has not been established, but should become the norm for operational research, by which we understand research into how an intervention is implemented" [12]. The reference to operational research generates further considerations.

Translational research and operational research

According to The Operational Research Society "Operational research (OR) is the discipline of applying advanced analytical methods to help make better decisions. By using techniques such as problem structuring methods (sometimes known as "Soft OR") and mathematical modelling to analyse complex situations, operational research gives executives the power to make more effective decisions and build more productive systems based on: more complete data; consideration of all available options; careful predictions of outcomes and estimates of risk; the latest decision tools and techniques" [13].

The absorption of different methodologies and a multidisciplinary approach are an enhancement, but care should be taken to avoid the risk that definitions and categories become loopholes through which to circumvent legal obligations or ethical principles. Particularly in emerging or developing economies where regulations and controls are less strict, there is a possibility that ethical assessments envisaged in regulations may be eluded by branding what are effectively clinical trials as "operational research" [14].

Requirements and problems

A careful and thorough analysis in "Life cycle of translational research for medical interventions" by Contopoulos Ioannidis and co-authors identified some of the requisites needed to promote translational research. They note in particular that "Discovery of new substances and interventions remains essential, but proper credit and incentives should be given to accelerate the testing of these applications in high-quality, unbiased clinical research and the replication of claims for effectiveness" [15]. Moreover, "multidisciplinary

collaboration with focused targets and involving both basic and clinical sciences should be encouraged" [15].

These objectives can be achieved in various ways. Ledford, for instance, suggests "4 ways to fix the clinical trial": "recruit early, skip animals; use models; alter course (use adaptive trials)" [5].

The route to a faster transition from research to application may be complicated if researchers are not sufficiently familiar with how to address the issues of translational research: "Many of us would readily claim to be translational researchers, but, in reality, very few of us know how to navigate the translational pathway – we are very comfortable speaking the language of the lab but have a quite limited understanding of the plethora of legal (how to secure a patent), financial (how to raise money to develop our intellectual property), regulatory (how to interact with a regulatory agency) and clinical (how to recruit subjects for a clinical trial) issues that must be considered before we get anywhere near a new therapy" [16].

The infrastructures

In 2006 the European Strategy Forum on Research Infrastructures (ESFRI) was asked by the European Commission to draft a European "road map" for Research Infrastructures (RI) [17]. The report drew attention to the importance of RI in the biomedical field, particularly translational research. The Council of the European Union subsequently issued a Regulation that creates a single legal foundation to facilitate the creation and operation of RI in the form of a European Research Infrastructure Consortium (ERIC) [18], which entered into force on 28 August 2009. This specific legal form is designed to facilitate the joint establishment and operation of research infrastructures of European interest.

One of these infrastructures, as we have already seen, is EATRIS [19], whose objective is to promote the process of translating the results of research into novel strategies for the prevention, diagnosis and treatment of diseases of particular public health and economic importance, which it does through a European network of national centres of excellence and high technological impact. It assists academic institutions in the process of translating research results into new approaches to the treatment, prevention and diagnosis of diseases with a high socio-economic and health impact and offers industries the chance to use highly sophisticated and advanced facilities as part of projects that are of special interest from a public health aspect. In other words, EATRIS supports translational research projects by supplying an efficient and integrated network of services to accompany an untested medicinal product (proof-of-principle) up to phase I and phase II trials with human subjects.

In 2010 the ISS was formally invited by the Ministry of Health, in agreement with the Ministry of Education, University and Research, to coordinate the Italian arms of EATRIS and other infrastructures: the European Clinical Research Infrastructures Network (ECRIN) [20] and Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) [21].

ETHICAL PROBLEMS

Translational research poses several ethical problems, many of which are common to all trials involving human subjects. In the case of translational research, however, these problems differ in both form and complexity.

Ethical reviews of research projects often tend to focus particularly on informed consent and other formal aspects, such as the protection of personal data. For example, the paragraph headed "Translational research" of a manual dealing with the ethical aspects of drawing up trial protocols identifies three particular areas of interest: "kinds of public/private collaboration that produce serious conflicts of interest", "reduction in funding for undirected basic research" and "personal data protection" [22]. Naturally, these three are not the only ethical questions encountered in the field of translational research; given that it aims to reduce the duration of the research phase, one of the key problems is undoubtedly that of possible risk to participants.

The risk to participants

A faster transition from research to clinical practice could lead to a lowering of safety barriers and an increase in risk.

Solid parameters are therefore necessary to ensure appropriate safety levels; clear indications are needed as to which laboratory data and which trial models should be acceptable as the basis for moving forward from basic to clinical research.

As a general rule, if there is no adequate evidence of benefit for the patient, no more than so-called "minimal" risk should be acceptable. "Minimal risk" has been variously defined: one frequently cited definition is to be found in the Code of Federal Regulations, which states that a risk is "minimal if the "probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or physiological examinations or tests" [23].

Kimmelman and London identify some aspects that are particularly important when assessing risks and benefits:

- "ethical judgments about risk, benefit, and patient eligibility in clinical trials hinge on predictions about harm, therapeutic response, and clinical promise;
- predictions for novel interventions in preclinical stages of development suffer from two problems: insufficient attention to threats to validity in preclinical research and a reliance on an overly narrow base of evidence that includes only animal and clinical studies of the intervention in question (evidential conservatism);
- to improve ethical and scientific decision-making in early phase studies, decision-makers should explicitly attend to reporting quality and methodological features in preclinical experiments that address threats to internal, construct, and external validity;
- decision-makers should also use evidence that sheds light on the reliability of causal claims embedded within a proposed trial. This evidence can be gathered from outcomes of previous trials involving agents targeting related biological pathways (reference classes)" [24].

Expected benefits

Risks and benefits are closely linked, but the objective of moving from research to practice – in other words, to generalizable knowledge – must not be allowed to compromise the cornerstone of trials involving humans, namely that the well-being of participants in trials must always come before the potential benefit to the community of an advancement in knowledge. Article 6 of the Declaration of Helsinki, for instance, states that: “In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests” [25].

Informed consent

The question of direct benefits is one of the issues that must be made clear when participants are being briefed prior to giving signed consent. As already noted, informed consent should never be a mere bureaucratic formality.

One of the questions that makes informed consent so important in translational research is the need to avoid what is known as a “therapeutic misconception”. This problem came to light in the 1980s during studies coordinated by Loren Roth [26, 27]. “At its core Therapeutic Misconception (TM) involves patient/participant’s failure to recognize how personal care may be compromised by research procedures. (...). (T)his core concept of TM can appear in two ways: 1) an incorrect belief that the patient/participant’s individualized needs will determine assignment to treatment conditions or lead to modifications of the treatment regime (TM1) or 2) an unreasonable appraisal of the nature or likelihood of medical benefit from participation in the study, due to misperception of the nature of the research enterprise (TM2)” [28].

Possible manipulation for commercial purposes: translational research in reverse

Informed consent is also important in contrasting possible manipulation for commercial purposes. A comment published in *Nature* on a well-publicised incident in Italy concerning a supposed treatment with mesenchymal stem cells, warned against “translational research in reverse”: “Industry has not yet generated conclusively proven medicinal products or major novel technologies to better harness the biology of Mesenchymal Stem Cells (MSCs). However, commercial interest has profoundly influenced the definition of these cells (and of their clinical potential) within the scientific community. This is translational medicine in reverse. Commercial products have been converted into scientific concepts. It highlights an important dark side of the commercialization of science” [29].

Ethical principles and new paradigms

Some authors feel that the ethical challenges posed by translational research are so important that it is time to formulate “a new conception of clinical research ethics” [30], in other words, a paradigm shift. “Medical research is widely thought to have a fundamentally therapeutic orientation, in spite of the fact that clinical research is thought to be ethically distinct from medical care. We need an entirely new conception of clinical research ethics – one that looks to science instead of the doctor-patient relationship” [31].

The statement that we need to “(look) to science instead of the doctor-patient relationship” may seem puzzling, and rightly so. It must not be allowed to turn the foundation of research ethics on its head: as already noted, the interests of the participants in trials must always have priority over those of the community in terms of improved knowledge.

As mentioned above, the problems posed by ethics in translational research are common to much of research with human subjects. There is thus no need for a new ethical approach: the principles established for biomedical ethics are amply sufficient.

There is an increasing tendency to link the terms “ethics” and “bioethics” with adjectives, as in “pragmatic bioethics” [28], “applied bioethics” [32] and even “synthetic bioethics” [33] (with reference to “synthetic biology” [34]), as well as “translational ethics” [35]. The latter expression is somewhat baffling if it is intended to reflect the proposal (typical of sociobiology, for instance) [36] to found ethics on facts, in other words to “translate” facts to principles. Instead we should encourage “translational ethics” as meaning the translation of knowledge to practice: “Much as translational research attempts to connect the laboratory scientist’s work to its implications for patient care, translational ethics focuses on bringing ethical scholarship into the sphere of personal and public action” [35].

While translational research does not need to investigate novel routes to ethical reviews, it does perhaps call for the application of logic to identify the right procedures by applying the basic ethical values of research with human subjects to the specific context.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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