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A few ethical issues in translational research for medicinal products discovery and development

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Abstract

The results obtained with basic research showing significant therapeutic promise are often not translated into clinical applications. The purpose of translational research is to favour the transition of basic research to application at the patient's bedside, and from here to routine clinical practice (without excluding the opposite pathway, in which the evidence generated by clinical practice helps to guide research). Although translational research can provide patients with valuable therapeutic resources, it is not risk-free. The most significant ethical issues in translational research on medicinal products derive from the risk of the intention to shorten the timeframes for the application of the results of the research making the scientific methods adopted and the regulatory requisites to be satisfied along the long path from the bench to the patient's bedside less rigorous. This is also relevant during pandemics when shortening the timeline from basic research to bedside is even more crucial. It is therefore necessary to establish defined and agreed requisites in order to guarantee the ethicality of translational research, by promoting the good of individuals and minimising the risks.

Key words

- ethics
- human experimentation
- risk
- translational research

WHAT IS TRANSLATIONAL RESEARCH?

Translational research has been defined in many different ways. According to the American Physiological Society, translational research promotes "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" [1]. Indeed, many scientific discoveries never go beyond the laboratory bench and are failing to be translated efficiently into tangible human benefit. Translational research aims to overcome this situation.

The objectives of translational research are: i) to translate scientific knowledge from laboratory and preclinical research to clinical research on human subjects; and ii) to transfer the knowledge generated in biomedical research into clinical practice [2].

The "translational research" debate has ranged for a long time and has been particularly lively since the 1970s [3]. A number of definitions of "translational research" have been put forward [4]. Generally speaking, the most frequently used expression and that summarises the various different definitions is "from bench to bedside". Indeed, "a translational researcher is someone who takes something from basic research to a patient and measures an endpoint in a patient" [5].

The European Society for Translational Medicine (EUSTM) defines translational medicine as an "interdisciplinary branch of the biomedical field supported by three main pillars: benchside, bedside and community. The goal is to combine disciplines, resources, expertise, and techniques within these pillars to promote enhancements in prevention, diagnosis, and therapies" [6].

With a broader outlook, translational research is "a dynamic and iterative process that includes synthesis, dissemination, exchange and ethically sound application of knowledge to improve the health (…), provide more effective health services and products and strengthen the health care system" [7].

The definition given by the American Physiological Society [1] also stresses the fact that translational research must not exclude the opposite pathway, on the basis of which the experience obtained through clinical practice can guide the developments of research [8].

Favouring the transition from laboratory data to practical application is necessary in all areas of biomedical research, but it is particularly important in the case of

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medicinal products, including vaccines, discovery and development. As is well known, there is a particularly long interval between basic research and the registration of a new medicinal product: this can be to the detriment of patients, especially when there are no alternative treatment options available or during epidemics as in the current case of SARS-CoV-2.

The case of vaccines, however, has some peculiarities that differentiate it from clinical trials of medicinal products. In particular, the spread of SARS-CoV-2 has reopened a heated debate on the possibility of authorizing and carrying out "challenge trials". Human challenge studies involve the deliberate infection of healthy volunteers. Such studies can be faster to conduct than vaccine field trials, in part because far fewer participants need to be exposed to experimental vaccines in order to provide preliminary estimates of efficacy and safety. The World Health Organization [9] has provided conditional approval to this extraordinarily contentious practice of 'challenge studies' for Covid-19 vaccines. However, challenge studies are difficult to admit due to serious ethical issues.

The path of translational research starts from laboratory research and reaches clinical application. Hence, it also includes animal experimentation. This contribution, however, focuses on human experimentation, from the "first in man" phase to the commercial availability of a new drug: it is in human experimentation, in fact, that the most relevant ethical problems arise.

TYPES AND PHASES OF RESEARCH

The pathway that research takes from the lab through to clinical application can be split into a number of stages. A number of different classifications have been proposed on the basis of different criteria.

One reprocessed approach [10] based on the classification put forward by Stokes [11] sees two orthogonal axes *(Figure 1)*. The horizontal axis represents relevance to immediate application. The vertical axis represents relevance to the advancing of knowledge. The area between the two axes has been split into four quadrants. The quadrant that is least relevant with regard to both immediate application and the advancing of knowledge constitutes the "waste quadrant", and is home to those research projects that do not make significant contributions to either the advancing of knowledge, or immediate application. The quadrant corresponding to high relevance to immediate application but little relevance with regard to the advancing of scientific knowledge is known as the "Doll quadrant", because of Richard Doll's work with Bradford Hill to identify smoking as a cause of lung cancer. The quadrant corresponding to the area of high relevance to advancing of knowledge, but poor relevance to immediate application, is known as the Curie quadrant, referring to the importance of the research Marie Curie conducted on radiation. The quadrant referring to the area of high relevance for both immediate application and the advancing of knowledge is known as the "Pasteur quadrant", as the scientific knowledge generated by Louis Pasteur had an enormous impact in reducing the morbidity, mortality and economic costs of infections. Translational research falls in this quadrant.

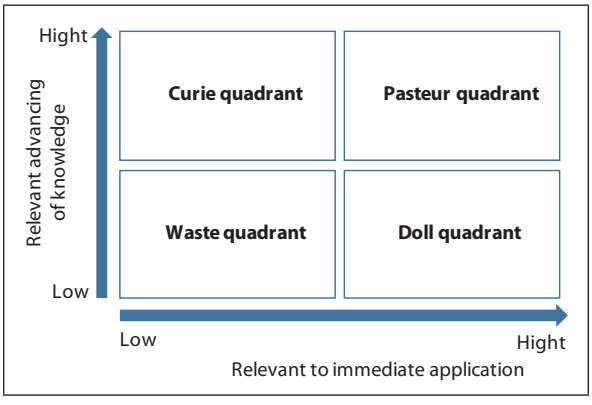

Figure 1
Quadrant model of scientific research.

The different interpretations of the development of research also translate into different interpretations of the role of translational research. Three major "families" of interpretations can be identified [12]:

1. the "gap" model, which has adopted, above all, by the "Clinical Research Roundtable" (CRR) working group [13]. According to this model, translational research bridges the gap between basic knowledge and clinical research in order to translate the knowledge generated from basic research into benefits for patients and / or the general population;

2. the "continuum" model corresponds with the interpretation given, for example, by Khoury *et al.* [14]. According to this model, basic research and clinical research are part of a same process in which phases are relatively continuous. In this perspective, the advancing of knowledge is translated through a "continuous research spectrum and phases in this continuum are labelled by common setting or research methods" [12];

3. the "mixed" model interprets the initial phases (basic research) in the same way as the "gap model" and the later stages of applied research in the same way as the "continuum" model [15].

ETHICAL ASPECTS

In the debate on translational research, significant space is dedicated to research organisation and management, for example regarding funding and staff training. For example, according to the abovementioned "Clinical Research Roundtable" (CRR) working group, the shortcomings in the transfer of the knowledge obtained with basic research to application are due to "2 major obstacles, or translational blocks: impeding the translation of basic science discoveries into clinical studies and of clinical studies into medical practice and health decision making in systems of care" [13]. According to the CCR, these two obstacles are associated with four "central challenges facing clinical research at present", namely "public participation, information systems, workforce training, and funding" [13].

Although the organisational and managerial aspects are relevant, in this paper we intend to focus in par-

ticular on the aspects that are most important from an ethical standpoint. It goes without say that the organisational and managerial aspects are closely intertwined with the ethical aspects [14]. For example, analyses of translational research promotion policies often reveal a need for funding: it would be important to adopt a national investment plan for research. However, without playing down the importance of adequate investments, the efficacy of translational research depends above all on the capacity to draw new lines and innovate, and this has a significant ethical relevance. This is particularly important in the case of research for new medicinal product discovery and development, where, despite disposing of significant funding from large companies, some of the many research projects that prove to be fruitless could, in actual fact, lead to useful applications if developed appropriately.

At the same time to make available new drugs and vaccines in an equitable way requires considering the so called "innovation science": to be successful in a system innovation requires precise reflections, planning and implementation policies.

Innovation Science encompasses a broad space [15]. It can contribute to the improvement of translational research by moving from a "hardware" approach (by restructuring organisation charts, upgrading procedures, etc.) to a "software" one (which reflects the complexity of the system and respect its resilient features, which often appear unexpectedly, arising from interaction of smaller or simpler entities). In this perspective, we might adopt new models that appreciate the complexity of the systems ad understand that changes is always unpredictable and needs to be tailored to the setting [16].

In other terms, the traditional conception of medical knowledge as a linear pipeline moving from evidence created in the laboratory through clinical trials and finally, via new tests, drugs or vaccines into clinical practice, is no longer sustainable. Complexity science forces us to consider the dynamic properties of the systems and the varying characteristics: the health system is probabilistic and stochastic rather than strictly deterministic, and often the characteristics of the components are secondary to the relationships of the components themselves [17].

Without playing down the ethical and non-ethical relevance of general policy, the most significant ethical issues in translational research on medicinal products derive from the risk of the intention to shorten the timeframes for the application of the results of research making the scientific methods adopted and the regulatory requisites to be satisfied along the long path from the bench to the patient's bedside less rigorous [18]. This could expose the subjects taking part in the research to undue risks. This is a crucial topic, with many different facets [19]:

1. *The safety and welfare of the subjects taking part in the study*. The researchers are under obligation to put patient welfare before any interest regarding the advancing of knowledge, society or profits;

2. *Direct and indirect benefits*. As recognised in the World Medical Association's Declaration of Helsinki (art. 8), "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" [20]. However, the precedence of the research subject's welfare over the interests of science or society does not, in any way, preclude the possibility of the participants obtaining direct benefits. In these circumstances, the need to analyse and restrict the potential risks is particularly important.

3. *Proportionality between risks and benefits*. All research involves risks. One crucial step, in which due caution is required, is the transition from laboratory research and/or research using animal models to trials on humans. It goes without say that the risk level is different in different studies and risks and benefits have to be balanced correctly. In special situations (for instance serious diseases for which there are no efficacious therapies available and epidemic situations), risk levels that would be unacceptable in other circumstances are permitted. Striking this balance is made difficult by the unpredictability that characterises all research. In this context, it is dutiful to guarantee special protection for individuals in conditions of particular vulnerability.

4. *Doctor-patient relationship*. In the case of translational research, in which the objective of the practical application of the research takes precedence, special attention must be dedicated to the relationship between doctor and patient, when providing the patient with information and the procedures required to obtain consent. Although the requisites set forth in the 3 previous points refer in particular to the ethical principles of beneficence and non-maleficence, the doctor-patient relationship, information and consent refer, in particular, to the ethical principle of autonomy [21].

5. *Equality of access*. When promoting the applicability of the results of the research, it is necessary to adequately consider access to the applications and avoid discrimination. This corresponds to the ethical principle of justice [21].

6. *Integrity of the research*. Translational research must always comply with the principles of research integrity. Research Integrity may be defined as adherence to the ethical principles, rules and professional standards essential for the responsible conduct of research [22]. Research Integrity is about getting to the scientific knowledge using the highest scientific, professional and ethical standards. Ethical practice, honesty, trustworthiness, and high regard for the scientific methods are essential attributes of any scientist with an interest in conducting research that benefits mankind. For research institutions, integrity is about ensuring commitment to creating an environment that promotes responsible conduct by embracing standards of excellence, trustworthiness, and lawfulness in the conduct of research by staff and all members affiliated to the institution. The term "Responsible Conduct of Research" (RCR) is often used by institutions to refer to a wide range of areas of research compliance [23].

7. *Conflict of interest*. Due to its nature, and especially for the potential commercial repercussions, translational research is particularly subject to the risk of conflicts of interest. A conflict of interest occurs when professional judgement regarding a primary interest (the

health of a patient, the validity of a study or a product, the truthfulness of the results of a study, etc.) is potentially influenced by a secondary interest, such as economic gain or personal advantage. Conflict of interest is therefore a condition (and not necessarily a behaviour) that could compromise the autonomy of a researcher and the impartiality of his/her professional actions.

8. *Need for monitoring*. In translational research, it is particularly important not only to assess protocols thoroughly, but also to provide constant monitoring, by qualified staff, throughout the conduct of the study. Special vigilance is required in this sense as the intention to obtain useful applications could lead some to be less rigorous on a methodological level or even to falsify data.

CONCLUSIONS

The ethical assessment of the risks and benefits of translational research must be performed on a case-by-case basis, considering the circumstances and the added value that it is expected the new medicinal product will bring (or, in general, a new therapeutic resource) over what is already available [24].

Translational research is not a set of methods and skills, but a strategy that requires experience and coordination. It is not a sequential activity, but a constant interaction.

Translational research requires cooperation between the academic and industrial worlds and needs a favourable administrative and political framework, whilst avoiding undue conflicts of interest: the primary objective must be the patient's welfare.

Therefore, in translational research, particularly stringent ethical requirements must be adopted and ethics committees can play a crucial role in guaranteeing the welfare and rights of the individuals taking part in the research.

The CoViD-19 pandemic has made it even more evident the importance of developing and making new medicines rapidly available. Moments of crisis are rarely good moments to develop ethics. However, it is necessary to question oneself on criteria and procedures, without derogating from the safety requirements for patients and rigor in the scientific method. An international conference could be important to define shared criteria, also for the purpose of any regulatory adjustments.

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