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Innovative therapies: general aspects and ethical criteria for evaluating protocols

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Abstract

There are many ways of interpreting the notion of "innovation" with reference to therapeutics. The term is generally given a wide meaning, encompassing anything that brings something new. From the ethical point of view the definition of "innovation" is of key importance, for example when dealing with a major problem such as the evaluation of protocols that propose "innovative" therapies. There is currently debate as to whether this should be accomplished using the same procedures typically applied to experimental research protocols, or by following quite different procedures when "innovation" is involved. The present article offers an overview of the notion of "innovation" in the context of biomedical research, together with some considerations and proposals for evaluating it from the ethical viewpoint. ***Clin Ter 2013; 164(1):e53-61.*** **doi: 10.7417/CT.2013.1522**

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What is "innovation"?

The Greek word νέος derives from the Indo-European "neuos", meaning young, new, or fresh, but also unexpected.

The word "innovation" first appeared in English in the mid-sixteenth century. According to Merriam Webster's dictionary it means "1) the introduction of something new; 2) A new idea, method or device - Novelty" (1).

The "ISDB Declaration on Therapeutic Advance in the Use of Medicines" adopted in Paris on 16 November, 2001 by the International Society of Drug Bulletins (ISDB) (2) states that "the term 'innovation' covers three concepts": the "commercial concept" ("any newly marketed me-too product, new substances, new indications, new formulations, and new treatment methods"), the "technology concept" ("any industrial innovation, such as use of biotechnology, or the introduction of a new substance delivery system (patch, spray, etc.), selection of an isomer or a metabolite") and "the concept of therapeutic advance" ("a new treatment that benefits the patient when compared to previously existing options").

The Declaration also offers proposals "for identifying therapeutic advance", identifying three fundamental aspects: efficacy, safety and convenience, in regard to each of which the Declaration provides practical suggestions.

With regard to efficacy, the Declaration states that: "the efficacy of a new drug intervention should be assessed in terms of overall mortality where relevant, morbidity, and quality of life as assessed from the patient's perspective. Therapies for chronic conditions require long-term studies. Comparative trials assessing the superiority of an intervention are required when there is an adequately tested treatment".

With regard to safety: "the following are required: well designed pharmacovigilance studies; long-term, large, randomised controlled trials with overall mortality as the main endpoint for assessing safety of prophylactic interventions".

Where convenience is concerned, the Declaration states that: "Before marketing, studies should be undertaken to show adequate ease of use and adherence to the dose regimen together with studies showing that patients understand and can use the accompanying information. Medicines legislation should incorporate this requirement as soon as possible".

In fact not all potential types of "innovation" are of equal importance. Therapeutic innovation is certainly one of the more significant, and not only in scientific terms. Even in ethical terms there are many circumstances in which it would be unacceptable to place pharmacological and technological innovation on the same plane as therapeutic innovation. "Pharmacological innovation based on a new mechanism of action could even turn out to be therapeutically less effective than existing mechanisms: a new mechanism of action acquires therapeutic significance when it allows a new drug to act on patients who do not respond to standard treatments" (3).

It is also evident that the therapeutic value of a drug will depend on the availability of other products with which to compare it and will therefore vary over time. This is why the evaluation of a drug's therapeutic value is such a crucial factor and why the ISDB generally uses the expressions "comparative efficacy" or "relative efficacy".

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The notion of "innovation" is also important in relation to intellectual property, patents and commercialisation. Thomas Alured Faunce observed that "one would have expected to see a definition of innovation in the World Trade Organization's (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). No such definition exists. Likewise, the concept is rarely, if ever, defined in legislation or policy documents" (4). It should also be noted that, although closely related to concepts such as novelty and inventiveness that are central to intellectual property regulation, innovation operates in a distinctly different way. The qualities of novelty and inventiveness in products are formally assessed by patent assessors in accordance with established protocols. Innovation *per se* has not traditionally been part of the formal intellectual property evaluation process.

A brief look through eminent handbooks of the ethics of experimentation and their approach to "innovation" gives heterogeneous and occasionally surprising results.

"The BMA's handbook of ethics and law" published by the British Medical Association (BMA) has a chapter devoted to research under the title "Research and innovative treatment", suggesting that the BMA considers any research to be at least potentially innovative (5).

However, another wide-ranging and well known handbook, addressed to the US Institutional Review Boards, appears to suggest otherwise. It contains the statement: "The terms 'innovative therapy' and 'nonvalidated practice' describe activities that are designed solely to benefit an individual patient(s) but in which the ability of the activity to result in the desired outcome is to some degree unproven" (6).

Other publications adopt a different approach: the notion of "innovation" is frequently introduced by referring to the "Belmont Report" of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (7). This contains the statement that: "When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is 'experimental', in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project. Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects".

Referring to the Belmont Report, Robert J. Levine, coauthor of another US handbook (8), wrote: "This class of activities [described in The Belmont Report] is most commonly called 'innovative therapy'; I proposed that it should be called 'nonvalidated practice' because the defining attribution was not novelty; it was lack of validation (demonstration of safety and efficacy), and the Commission's reasoning about how to deal with such practices applies to diagnostic and to preventive measures, not only therapies". The expression "nonvalidated practice" had already been proposed by Levine elsewhere, including in a book that was widely read at the beginning of the 1990s (9), as well as in earlier essays, to which we shall return later.

Distinctions between "innovative treatment" and research are also found in other handbooks. One with a slightly more legalistic approach than those just cited contains the following sentences in the chapter headed "Informed consent to innovative treatment": "Doctors not infrequently offer patients new or unproven interventions as part of a patient's medical care. These situations are similar to research in that the patient is being asked to consent to something whose safety and efficacy have not yet been established. However, in the clinical context, the intervention is being offered because the doctor thinks it is the best choice for the patient; in research, by contrast, the goal is to develop generalizable knowledge. Because these situations differ from both ordinary medical treatment and formal research, they raise unique informed consent issues" (10).

If we accept this approach, the definition proposed by Patrick L. Taylor could be appropriate: "Innovative therapy is the name we give to novel medical interventions, radically different from the standard of care, provided in order to benefit a patient, rather than to acquire new knowledge. They are paradigm shifting, not incremental, responses to serious patient problems that standard medical care inadequately addresses. Innovative therapies are often devised by clinicians, not basic science researchers; they do not follow the linear model of basic research, to translation, to clinical research, to application. Instead, they come from thinking backwards from the patient's circumstances, and forward from deep knowledge of how the body functions, to challenge the limits of current mechanisms for effecting cures. This means therapeutic innovators often try to do what has been considered impossible" (11).

All of this clearly shows how problematic it is to attempt to identify the confines between "research" and "innovative treatment". It raises an additional question: whether or not "innovative treatment" should undergo a process of evaluation by the competent ethical committee similar to that applied to research protocols. The citation above suggests that the Belmont Commission's reply would be No. Before examining this aspect, however, it may be helpful to consider two preliminary factors: how to "measure" and how to "promote" innovation.

How can we measure "innovation"?

Few innovations bring radical changes (or, to use Khun's terminology (12), are paradigm-shifting): progress usually arrives one step at a time, but it is useful to "quantify" these steps as far as possible.

The problem is complex and has been examined amply in the literature. Although it does not lie within the aims of the present article some examples may nonetheless be useful, albeit without going into the technical details of algorithms. Two proposals will suffice, both elaborated by Italian researchers and both of which have roused considerable interest in recent years.

The first method (13, 14) starts by taking three key elements: "disease seriousness", "availability of treatments" and "therapeutic effect". Each element is further subdivided: disease seriousness, for example, is subdivided according to the seriousness of the disease, while the availability of treatments considers not only availability but also other factors such as the onset of resistance leading to insufficient responses to treatment. By collating the various combinations an evaluation of the level of innovativeness of each treatment is generated, which can be classified as "important", "moderate" or "modest".

The second method calculates the innovativeness of a drug on the basis of the results of "clinical efficacy" and "clinical effectiveness" (15). This algorithm is more complex than the one mentioned above and is based on the combination of a multitude of factors. The resulting score is highest for drugs that cure pathologies for which there exists no therapy or for which existing therapies are unsatisfactory, and lowest if the innovativeness is limited to improving an existing pharmaceutical preparation. The score is based mainly on the design of the research, the type of results achieved by the patient (cure, improvement in symptoms, etc.), the frequency and seriousness of adverse reactions reported, and many other factors.

The methods just described show that it can be relatively easy to attempt to quantify the "innovativeness" of a drug after its development, but "it can be difficult to recognise the magnitude of an innovation while a new treatment is being developed" (16).

How to promote "innovation"?

As for the preceding paragraphs, this problem also falls outside the scope of this article, but a few considerations are nonetheless in order.

Innovation can arise either revolutionarily (by a single transformation) or evolutionarily (by gradual change incrementally) (17).

To create incentives to spur on future innovation, governments and agencies should work with industry to create and adopt simple procedures that facilitate the development of new treatments.

The promotion of innovation has important economic and commercial implications. While innovations need to be protected by means of patents, it should also be recognised that, as Joel E. Hay observed, "Patents are antithetical to market competition. They reward innovation by having the government patent office grant time-limited monopolies to the patent holders […]. The problems associated with the patent system are particularly acute in an area such as pharmaceuticals, where lives are needlessly lost, and patients needlessly suffer not because the patient or the payer can't afford the medication cost, but because the patient (or his or her insurer, government program, or international aid agency) cannot afford the marginal cost of the medication plus the monopoly markup established to reward innovation" (18).

Additionally, in the pharmaceutical sector as in other sectors, innovations are not always, or not easily patentable. For example, aspirin and certain antibiotics are considered among the most important drugs developed during the last century, but their development lagged for decades because there was no potential patent reward for pharmaceutical companies to establish and market a new use of a product that any company in the world could already sell generically (19, 20): "(had) they been developed and marketed as quickly as statins or H2 receptor antagonists, millions of lives and billions of dollars could have been saved" (18).

The "Innovative Medicines Initiative" (IMI) is one of the broadest-ranging and better known initiatives in the field of innovative drugs in Europe (21). Established by the Council of the European Union on 20 December 2007 (22), "IMI is a unique pan-European public and private sector collaboration between large and small biopharmaceutical and healthcare companies, regulators, academia and patients. The aim of IMI is to support the faster discovery and development of better medicines for patients and enhance Europe's competitiveness by ensuring that its biopharmaceutical sector remains a dynamic high-technology sector. The Innovative Medicines Initiative will ensure that Europe's biomedical sciences receive targeted strategic support for the benefit of patients, as well as the scientists and citizens of Europe. IMI proposes a number of clear, practical paths that will accelerate the discovery and development of more effective innovative medicines with fewer side-effects. IMI will implement innovative Patient Centred Projects that address the principle causes of delay or bottlenecks in the current biomedical Research and Development (R&D) process" (23). The Strategic Research Agenda (SRA) (23, 24) describes four strategic areas ("Four Pillars") that address the principal causes of delay in the biomedical R&D sector: predicting safety, predicting efficacy, bridging gaps in knowledge management and bridging gaps in education and training.

The Initiative has also incurred criticism: eminent reviews have expressed perplexity regarding this initiative in particular (25) and European policy in the sector in general (26). However, it must be recognised that results have been achieved, as confirmed in the Annual Activity Reports (27).

The IMI is destined to undergo marked changes, particularly within the workings of the European Union Framework Programme for Research and Innovation. As part of the "Horizon 2020" programme (scheduled to run from 2014 to 2020) the Innovative Medicine Initiative will be implemented through public-private partnerships (PPPs). Selection of PPPs "will be based on a set of clearly defined criteria, including the added value of action at Union level, the scale of impact on industrial competitiveness, sustainable growth and socio-economic issues, and the long-term commitment from all partners based on a shared vision and clearly defined objectives" (28).

On the subject of EU policies aimed at encouraging innovative medicine, another important factor to remember is that further marked changes will be introduced once the European Commission completes the process of reviewing Directive 2001/20/EC (29). The new document proposed by the Commission will take the form of a Regulation. This will ensure that the rules for conducting clinical trials are identical throughout the European Union. In particular, it will make it easier to conduct multinational clinical trials in Europe. Some concrete proposals are: an authorisation procedure for clinical trials which will allow for a fast and

thorough assessment of the application by all Member States concerned and which will ensure one single assessment outcome; simplified reporting procedures which will spare researchers from submitting largely identical information on the clinical trial separately to various bodies and Member States; more transparency on whether recruitment for participating in a clinical trial is still ongoing, and on the results of the clinical trial; the possibility for the Commission to conduct controls in Member States and other countries to make sure the rules are being properly supervised and enforced (30). The legislative proposal will now be discussed in the European Parliament and in the Council. It is expected to come into effect in 2016.

Against this background it is important to consider that the promotion of innovation is an extremely complex affair in which numerous and conflicting interests converge. Just how complex can be illustrated by the fact that in the second half of the 1960s 92 new drugs were produced in France and 94 in the US: between 1990 and 1995, however, 85 were produced in the US and just 14 in France. This was largely "the impact of price controls. The French system aims to force the lowest possible unit price for pharmaceuticals, and, in pursuit of this, it takes very deliberate aim at innovation. When a genuinely new product is approved, its price is set based, in part, on its expected sales volume. If the sales exceed expectations, the maker is required to cut the price to offset the incremental costs to the government. In other words, innovation is punished if it is successful" (31).

The different paths of innovation

While wide-ranging and valid programmes to address a multitude of situations, such as those mentioned above, are helpful, it must also be borne in mind that innovation proceeds in different ways in different sectors.

In some fields, such as oncology, there is close synergy between innovative therapies and research: innovative therapies are often prompted by the failings of existing therapies. The major failings are noted and extensive clinical trials are launched involving large groups of patients; if the results are promising they are incorporated into current practice.

In other sectors progress may follow a different path. In surgery, for example, innovations are frequently decided during an intervention on a single patient in an emergency situation (in other words, very rapidly). Such decisions have to be taken if things are not going according to the usual plan and, faced with the unexpected, consolidated guidelines have to be abandoned. Only subsequently (and not always) is research conducted with a sufficient number of patients to allow a statistical evaluation (32).

Naturally, numerous situations will fall between these two examples of oncology and surgery, involving not only other medical specialisations but the whole sector of patient care (33).

Innovation, comparative, non-inferiority and other types of research

Mention has already been made of the widely proposed distinction between "innovation" and "research", and this will be addressed later.

But first it must be recognised that research frequently leads to the discovery or invention of "novelties" that may not be classifiable as "innovation" as defined earlier.

There are also other types of research that are not designed for the purpose of innovating, but perhaps adopt different strategies aimed at finding new uses for existing drugs. Thus the fact that a research programme is not planned to lead to "innovation" does not necessarily mean that it is not useful. The category of research not designed to produce "innovations" includes both studies that may potentially lead to ground-breaking results and others that are intrinsically less useful and may even raise legitimate scientific and ethical concerns.

Comparative research

Much attention is today directed to so-called "Comparative Effectiveness Research" (CER). The Institute of Medicine (IOM) defines CER as follows: "Comparative Effectiveness Research (CER) is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels" (34). Put very briefly, one could say that: CER is directed mainly towards healthcare decision-makers in both the practical clinical and health policy fields; it compares at least two alternative procedures; it compares the risks and benefits in populations and sub-populations.

Although CER seldom produces "innovations", it would be wrong to dismiss it *a priori* as useless. There are, however, those who question its usefulness: "Surprisingly little attention has been paid to what we believe is the most critical question facing CER: Will its results significantly improve the quality and safety of the health care received by the average patient? […]. Though we agree that the need for CER is clear, many of the assumptions regarding the most important aspect of such research – the ultimate implementation of its findings into health care – have little empirical support" (35). Notwithstanding this it cannot be denied that some CER programmes are helpful.

One instance of research based on comparisons, albeit not classifiable as CER according to the IOM definition, is required by many regulatory authorities prior to the approval of biosimilar drugs. The possibility of producing and using biosimilar drugs is certainly useful, and authorisations for the commercialisation of these medicines are based on research that, while not conforming to the above definition of CER, is nonetheless comparative. In order better to understand the significance of biosimilar drugs it may be useful to recall briefly the relationship between biological and biosimilar medicines.

Biological medicines are drugs whose active principles are produced naturally by a biological organism, or derived from a biological origin using biotechnological procedures (e.g. recombinant DNA, monoclonal antibodies, etc.). Unlike drugs produced by chemical synthesis, the characterisation and quality control of biological medicines require not only a series of physical-chemical-biological tests but also the provision of specific information regarding the production process, on which the molecular structure of these products closely depends. Because of the intrinsic variability of molecules and the complexity of the production techniques, biological drugs are particularly difficult to characterise and to reproduce, to the extent that differences can be found even between lots of a single product (36). This is why the regulatory authorities impose very strict controls on the procedures for preparing biological drugs (37, 38). On expiry of the patents for these biotechnological medicines, all pharmaceutical companies have the right to produce and market biological medicines with the same characteristics as the biological drug patented by another company. These biological products, whose active principle is similar but not identical to the reference drug, are known as "biosimilars". The term "biosimilar" thus refers to medicines that are similar to a previously authorised reference biological product (originator) on which the patent has expired: the active principles of both products are similar but differences may exist in the raw materials used or in the production processes (39, 40). The term "biosimilar" is therefore similar to but different from the expressions "generic medicine" or "equivalent drugs" used to describe chemical drugs. Unlike biosimilars, generic or equivalent medicines have the same qualitative and quantitative composition of active substances and the same pharmaceutical form as the originator (41). Approval of the generic form of drugs produced by chemical synthesis is based on the assumption that the two molecules are equivalent. This can be confirmed by applying standard analytical procedures and bioequivalence studies. The generic approach cannot, however, be applied to copies of therapeutic proteins because of their complexity. Biological drugs are protein macromolecules in which even a minimal variation in the production process can lead to a substantial difference in efficacy. This is why the procedure for approving biosimilars is considerably more complex than that for generic drugs and calls for thorough and careful tests to compare quality, efficacy and safety (42). These comparative studies do not lead to "innovations" but there is no doubt that the availability of biosimilar medicines, as of generic drugs, is of considerable economic importance and has substantial effects on the accessibility of drugs.

Non-inferiority trials

Although non-inferiority (or equivalence) trials are fairly widespread, they frequently give rise to legitimate concerns from the methodological and ethical points of view. While CER may lead to innovations (at least in clinical practice or welfare), non-inferiority trials cannot really be considered to belong to the category of "innovation".

Non-inferiority trials are designed to show the efficacy equivalence of one active principle to another, usually already established. In fact, the absolute equivalence of two treatments cannot be scientifically demonstrated, and the term "equivalence margin" (i.e. the smallest clinically acceptable difference between the effects of the treatments) is therefore used in non-inferiority trials. In other words, non-inferiority trials are designed to show that one treatment is at least no worse than another treatment, within the non-inferiority margin. The smaller size of non-inferiority trials makes them especially attractive to pharmaceutical companies compared with superiority trials or placebo controlled trials (43). They are also economically preferable when marketing new drugs entering a crowded arena with established competitors. However, the condition of non-inferiority is clearly not proof of efficacy or effectiveness. For example, if A is as good as B, this does not mean that A and/or B is/are better than placebo. Non-inferiority trials are thus often criticised (44, 45). The Italian National Bioethics Committee (NBC), for instance, emphasises the poor scientific and ethical justification for non-inferiority trials, citing: the scarce scientific validity of the research, of their methodological-clinical interest and of the definitive guarantee of their efficacy (which is instead guaranteed by drugs that have already been tested and are available on the market); the potential "conflict of loyalty" for the physician, whose primary duty is to offer the patient a suitable treatment of proven efficacy (for which standard treatments offer guarantees that the drug on trial cannot); the lack of transparency regarding the informed consent given by the patient, who is often not provided with sufficient information on the nature of the planned trial. The NBC reasserts the principle affirmed in numerous international documents, namely that the specific interest of the patient should not be subordinated to any other interests, including commercial interests or those of the sponsor. The NBC particularly recommends that non-inferiority trials be presented in a more transparent manner and that ethics committees examine very carefully their design methodology, approving only "superiority" trials that can bring potential benefits to the participants and to future patients (46).

Drug repositioning: predicting new indications for approved drugs

The development of new drugs is an extremely long process (not less than 10-12 years) and often inefficient (it is estimated that only one out of each 5,000 or so new molecules that are synthesised becomes a drug). In addition, costs are enormous, and rising (in 2012 the development of a new drug costs at least 1 billion dollars; in 2010 the average cost was approximately 800 million) (47). For these reasons there is increasing interest in the possibility of identifying new therapeutic uses for drugs already approved and on the market: a number of existing approved drugs may prove effective therapy for diseases other than those for which they were approved (48). To this end various procedures have been tried, based on chemical, genetic and informatics studies, animal experiments and other types of research (49). One of the most original and promising methods is a completely computerised system known as "Train, Match, Fit, Streamline" (TMFS) (50). This method combines eleven different descriptors, which include shape and topology signatures, physicochemical functional descriptors, contact points of the ligand and the target protein, chemical similarity, and

docking score. The developers of this method have shown that it is remarkably accurate, giving few false positives or false negatives. Using the system they found, for example, that the antiparasitic mebendazole has the structural potential to inhibit VEGFR2 kinase activity and angiogenesis and therefore has unexpected anticancer properties.

What is the relationship between "innovation" and "research"? Some ethical criteria for the evaluation of protocols

As noted above, the Belmont Report drew a distinction between knowledge-oriented research and both innovative and accepted medical practice. The Commission that drew up the Belmont Report (established by the President of the United States and operative between 2 July 1974 and 8 April 1979), had two objectives: to identify the fundamental ethical principles surrounding the conduct of research with human subjects; to develop guidelines to ensure that trials were conducted in agreement with those principles (51). The principles thus identified (respect for persons, beneficence, justice) were then extended from the specific case of research to the entire field of medical ethics (52).

Thanks to its importance and its timing, the Belmont Report subsequently inspired legislation and further documents, not only in the US. Since its publication enormous progress has been made not only in technology and knowledge but also in organisation, while the cultural context has also evolved. There has, for instance, been a substantial increase in the number of local ethics committees (which at the time the Belmont Report was published barely existed in many nations); the number of *ad hoc* commissions, working groups and committees producing guidelines or similar documents has likewise ballooned; the procedures for managing and interpreting risk and safety have evolved profoundly; the closer ties between research, industry and commercial exploitation have created new situations of possible conflicts of interest. Notwithstanding these changes, the distinction proposed in the Belmont Report is generally maintained and in many countries only research has been compulsorily subjected to precise rules and to review by Institutional Review Boards (IRBs) or similar authorities.

Research is regulated by precise rules

Research is much more tightly regulated than standard treatments, with a succession of barriers that range from reviews of proposals for funding, through approval by an IRB, to detailed requirements for informed consent and peer-review at the time of publication. The various rules and regulations provide patients who participate in clinical trials with a series of guarantees that are not usually available in ordinary clinical practice. As N. Fost put it: "a physician providing routine care has considerable liberty to experiment on his patients. This experimentation is commonly termed 'innovative therapy'. The central differences between innovative therapy and research are that, in the former, there is relatively no regulatory oversight and a minimal likelihood that generally applicable knowledge will result. In the trenchant words of Paul Lietman, 'As long as you promise not to learn anything from what you're doing, you don't have to go through an IRB' [...]. It might be said in response that the researcher has a conflict of interest in serving two masters: future patients versus the patient before him. It is this conflict that leads the physician/investigator to compromise the interests of his patient in the name of science, society and perhaps personal advancement. But the potential for these conflicts has been largely buffered in recent decades by the many layers of oversight in clinical research" (53).

The crucial question is therefore: should innovation be evaluated/authorised by an ethics committee in the same way that research is? If the answer to this question is in the affirmative, another one presents itself: which procedures should be followed? (54). If research and innovation were precisely identical, the discussion on evaluation procedures would be of little use; it would be enough to apply the usual evaluation criteria used for research, for which precise regulations (55) and guidelines (56) are available.

The clinical context surrounding innovative therapies is more flexible than that of research

There is another important consideration to be borne in mind when discussing whether or not innovative therapies should be subject to the same programme of reviews adopted for clinical trials. In the case of clinical trials not only the regulations and guidelines but also the protocols for their conduct are very strictly structured, partly so that the data they generate can be compared and generalised: they generally specify a precise, strict and rigidly fixed sequence of trials to determine safety and efficacy. Innovative therapies, in contrast, often emerge in the course of clinical practice and are thus regulated less by rules and guidelines than by the professional clinical ethics of the physicians and nursing staff in hospital wards. This does not mean that an innovative therapy is identical to current practice: indeed, it represents a clear break from routine practice, a paradigm change, a new approach.

This brings us back to the fundamental distinction made in the Belmont Report: innovative therapies, like the clinical practice from which they spring, are intended to benefit a particular patient; the researcher, on the other hand, is working towards a wider goal that not only seeks the benefit of individual subjects but is also designed to increase generalizable knowledge.

For a better understanding of the view taken by the Belmont Report it is helpful to recall that prior to drawing it up the Commission invited various experts to submit their opinions on the problems under review.

One of these contributions was written by Prof. John Robertson and its title is: "Legal implications of the boundaries between biomedical research involving human subjects and the accepted or routine practice of medicine" (57). The text draws a distinction between "standard medical practice" on the one hand, and "research and innovative therapies" collectively on the other, calling the latter "boundary activities". According to Robertson, the evaluation of risks involved in innovative therapies calls for "an examination of the risks created by boundary activities, the efficacy of current controls, and the incremental costs and benefits of additional controls". The professor continued, adding that

the risks can be grouped into two types. The first type is associated with clinical uncertainty, which in turn is the result of three main factors: general lack of knowledge; lack of the clinical proficiency that clinicians acquire with high case volume and experience; and ignorance of whether the intervention is indicated or contraindicated for various patient categories. The second type of risk is associated with the professional ambitions of researchers, which may cloud the search for the wellbeing of the patient. This, according to Robertson, means that research carries a further risk for patients/participants that is not present in innovative therapies: the researcher has a conflict of interests because his or her goal is to acquire generalizable knowledge that will benefit future patients, and this goal may conflict with the pursuit of the good of the patient before him or her. Therefore, according to Robertson: "research and innovative therapies are different; IRB review should not be required for innovative therapies".

Another contribution to the preparation of the Belmont Report was requested of Prof. Robert J. Levine, already mentioned earlier on the subject of the definitions of "innovation". Levine's point of view differs radically from Robertson's. According to Levine "innovative therapy is another form of experimentation" and therefore, "any innovative practice in which the deviation from customary practice is substantive should be conducted so that it most closely approximates the standards of good research [...]. It further means that the proposed innovative activity should be reviewed by an IRB" (58).

Risk and equipoise

Notwithstanding the difference of opinions that emerged during the debate, the approach adopted by the Belmont Report made a clear distinction between innovative therapies and both current clinical practice and research. Innovative therapies are nonetheless much closer to clinical practice than is research. Innovative therapies, like current practice, are focused on a single patient, with the difference that they seek new routes to achieve their goal and are therefore beset by considerable uncertainty concerning the risks and benefits that may ensue. Consequently, the less risky option may not necessarily be in the patient's best interest. When weighing the risks and benefits, the person undertaking innovative therapies may accept a very wide margin of uncertainty and choose a route about which little is known. In other words, innovation arises precisely when the "innovator" moves away from standard practice and accepts an unknown risk in the conviction that it may lead to an improvement for the patient. The "innovator" is thus not in a situation of equipoise.

The term equipoise was brought into the ethical debate in 1974 by Charles Fried to describe a condition that is scientifically and ethically necessary to the conduct of a clinical trial: the physician-researcher must be quite unbiased in his attitude to the therapeutic value of the experimental and control treatments being evaluated in a trial (59). However, this interpretation of equipoise as involving only the judgement of the physician-researcher, is ambiguous, as individual equipoise tends to be instable. The opinion of a single physician can change with each successful outcome for a patient, or when adverse events are suffered by another. The most widely accepted definition of equipoise was proposed in 1987 by Benjamin Freedman, who suggested the concept of "clinical equipoise" (or collective equipoise), according to which a randomised clinical trial is acceptable so long as the professional community has not reached consensus as to which is the best treatment for a specific pathology. Freedman thus considers medicine a social rather than an individual reality (60).

The person who embarks on an innovative therapy is in a condition of non-equipoise, at least at the outset. This is because at the start of an innovative therapy the risks are generally high, the benefits uncertain and scientific knowledge scarce. The relative weight of the three types of uncertainty (risk, benefits and knowledge) will vary: for instance, therapies with stem cells and, more generally, so-called "advanced" therapies (gene therapy, cell therapy, tissue engineering) (61), are based on a fairly substantial body of knowledge, but the potential risks are considerable. Later, if things go well, the risks will diminish, the benefits will become clear, knowledge will increase and the innovative therapy can enter current practice. However, it does not always work out this way, and the reasons why an attempt at innovative therapy may not lead to a new accepted practice are many. Failure may be due to excessive risks (in absolute terms or in relation to the benefits) or to the therapy not being effective, but other factors (including excessive costs) may also intervene.

Thomas Lee, David Torchiana and James Lock went so far as to affirm that to pursue only minimal risk and safety can have "perverse consequences", as it could deprive patients of better choices (62). There can be no doubt, though, that personal risk is a crucial factor that deserves maximum consideration, whether by an ethics committee or in any other way. In order, however, to avoid this consideration taking the form of an unrealistic demand that risks should be eliminated, the ethical appraisal must be both flexible in its judgement and strict when providing reference criteria. Flexibility means that when systems are available that are able to optimise safety and minimise risks, the ethical review can be less stringent. Strictness means not accepting a risk unless it is proportionate to the expected benefits and that benefits should be for the person directly involved and not a generic advantage for other potential or future patients.

Some operational criteria

In the light of the foregoing it is possible to identify some indispensable requisites for evaluating innovative therapies:

- Informed consent must be a priority consideration: innovative therapies are often proposed in response to situations of particular seriousness, in which the patient is particularly vulnerable and there are few alternatives. The risks, benefits and possible alternatives must be explained as clearly as possible, regardless of the uncertainties surrounding them.
- When evaluating an innovative therapy the individual patient must be the central figure, as is the case in clinical practice, where a single patient in care is the focus of attention, rather than the whole category of patients with

the same pathology. The informed consent procedure, the possible alternatives and the manner in which these are considered, must all be formulated with the single patient in mind.
- When evaluating the pros and cons the scientific data available in the literature and the rationale of the proposed therapy must be carefully examined.
- Any physician proposing an innovative therapy must be of proven and well documented competence.
- The healthcare facility in which an innovative therapy is administered must be adequate.
- Programmes to address issues of safety, risk management and adverse events must be in place.
- There must be appropriate structures and procedures to monitor efficacy.

There are several ways to evaluate and check the above requisites. Ethics committees can certainly play an important role in assessment and supervision, but their involvement may not be indispensable, particularly in emergency situations, when it is effectively impossible.

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