

PRINCIPLISM *VERSUS* UTILITARIANISM IN TRANSLATIONAL MEDICINE ETHICS

MIRCEA LEABU*

ABSTRACT. Translational medicine is a rather new research area, as it was mentioned for the first time in 1996, in the PubMed publication index, while bearing as a motto “From bench to bedside”. Its complexity and novelty manage to raise a series of problems, in both medical and bioethical terms. The intricacy of translational medicine resides in the implication of several related research areas, such as tissue engineering, gene therapy, cell therapy, regenerative medicine, molecular diagnosis etc, all of them aiming to orientate current biomedical knowledge toward new effective drugs and medical approaches, while the increase of patients’ beneficence is closely looked upon. The promises of several research areas in translational medicine draw certain pressures upon biomedical studies and researchers, pressures made by research policy makers, politicians, patients, entrepreneurs, and also by the civil society and which bring several ethical challenges to all the above-mentioned stakeholders. Therefore, making good ethical decisions is mandatory. In this paper, I wish to discuss translational medicine ethics from the perspective of principlism and utilitarianism and also suggest rationales for considering the two theories on bioethics as complementary rather than conflicting. A parallel shall be drawn between the four principles of bioethics (acknowledged either by the Anglo-American or by the European principlism) and utilitarian bioethics, which are considered mere tools serving the same purpose: patients’ welfare.

Keywords: bioethics, translational medicine, principlism, utilitarianism, ethical decision-making.

Introduction

I shall begin my article with a truism, for which I kindly ask the readers not to judge my approach too harshly. Throughout our entire life, existence gravitates toward three verbs. The first one is the verb **to be** and it begins its action before we can even become conscious of what is happening to us, which is our moment of birth (and, who knows, maybe even earlier). The second one is the verb **to have**, and it gradually insinuates itself into our lives, as we realize that *to be* depends on the possession of resources, or so it does in physiological terms mainly. Finally, we have the verb **to do**, and the following reflections try to address the interrelations between this last verb and the other two, in terms of ethical and deontological approaches.

* *Department of Cellular and Molecular Medicine, “Carol Davila” University of Medicine and Pharmacy & Department of Cellular and Molecular Biology, “Victor Babes” National Institute of Pathology, Bucharest, Romania*

Addressing the relationship between *to be* and *to do*, I may affirm it is accompanied by an intrinsic morality, even if we were to analyze it from the primitive perspective of an uneducated person for whom *to do* means “to make a living”. *Doing* in order to *be* involves a moral relationship, even without being one hundred percent aware of it. If we take the case of an educated person, whose *doing* could become the only reason for *being* (the ideal situation), i.e. one *is* in order to *do*, the impregnation with morality became obvious. The relationship between *to do* and *to have* needs to be qualified, and that claims the intervention of ethics. In my opinion, *to do* with the aim of gaining goods (that is as a reason of *having*) is a profoundly immoral attitude. Moral is *to have* as a consequence of *to do* (meaning to possess as a result of an activity performed in order to fulfill our human condition). For such an attitude to be embraced, an ethical education is needed along with the building of strong characters. Such an ethical education would provide with generosity the meaning of human existence.

Furthermore, I shall transfer the above comments from the personal life to the professional realm, by asserting that professionalism cannot be defined in the absence of the verb to do. No one can work in any profession without doing something for it every day. However, only he who does not work does not err. How to avoid making mistakes in a profession is taught by deontology, which guides us toward correctness. This field is necessary but not always sufficient though, particularly when it comes to very complex working areas. Therefore, ethics is once again needed, because it has the capacity to identify what is the right path to follow.

Once having considered the reflections above, we may return to the topic under debate: translational medicine and the ethical issues arising from its development. Due to its complexity (as we shall later see), translational medicine is one strong example of area where deontology is widely required, while ethics confers upon it the sufficiency to guarantee the right attitude for the professionals working under its umbrella, an attitude specific to a human being, according to its highest meaning.

Basics of translational medicine concept

This locution, “translational medicine”, is rather recent, appearing as such for the first time in PubMed in 1996 [1]. The coining of the term and its definition as a concept and research field were due to the attempt of rushing clinical applicability of basic research results and knowledge deepening in biomedicine. In the last fifty years, the development of our knowledge in medicine, at the cellular and molecular level, has grown exponentially. The scientific research results increase the knowing-how and the knowing-that [2]. That raises our concern about knowing-what is ethical to be done. The motto of translational medicine is „from bench to bedside”. Translational medicine could represent a subterfuge to reduce the pressure made on biomedical research in order to urge the clinical application. However, it could also represent a camouflage for speeding clinical tests in medicine under the pretext of still being a scientific research. In these circumstances, it is obvious that translational medicine is an area sensitive to the ethical issues.

It is difficult to trace a firm border between the basic research in medicine and translational medicine. The more difficult as, for the most promising research directions the translation of the results into the clinical practice (as shown the tests on laboratory animals and even the attempts on human subjects) was unconvincing and sent back to the development of the knowledge by basic research, to increase our understanding on biological events at the cellular and molecular level. Nevertheless, one issue is more or less vocally recognized: our knowledge is not developed enough in mechanisms governing the biological events exploited in the translational medicine areas to let us ignore the risks. Medicine professionals (researchers and clinicians) have to avoid events such as the deaths of Jesse Gelsinger [3] or Jolee Mohr [4], despite the investigation results having been different in the two cases. Therefore, risk management in translational medicine is a very important ethical issue [5].

The complexity of translational medicine resides in the various research areas subsumed, such as: gene therapy, tissue engineering, cell therapy, immunomodulation of the cell behavior and the interaction control of therapeutic bio-material with the recipient body, regenerative medicine and molecular diagnosis. It is easy to draw a conclusion by observing (even superficially) that all the mentioned research areas and the studying directions elicited by them are intertwined and cannot be considered independently. The translational medicine concept was coined precisely in order to overcome the temptation of artificially segregating the various research fields in biomedicine. Finally, the most up-to-date corollary target followed in current medicine is personalized medicine. Without reconsidering the old dictum, attributed to Armand Trousseau (1801-1867) and which states that “there are no diseases, there are only sick people”, we cannot think ahead and neither can we push forward the advancement of medicine.

Therefore, we are forced to insist on the importance of speeding our knowledge completion in medicine, especially in translational medicine, in order to increase our progress in making basic research results applicable into clinic as swiftly as possible. In other words, we are condemned to push ahead the development of a research domain highly sensitive to ethics (in both theoretical and applied forms), and we are constrained to find solutions for the wisest ethical decisions. Fortunately, bioethics (at present needed more than ever) has „anticipated” its own necessity and has consequently developed itself over time using respectable brains along the 20th century and, after World War II, its advancement was imposed by the historical events (social and professional ones respectively).

Principlism *versus* utilitarianism

There are several ethical theories applicable in biology and medicine. In this paper, I will approach the basics of two of them (as a matter of fact, the most commonly used ones) and their helpfulness in ethical decision-making: principlism and utilitarianism.

Essentially, principlism is grounded on four *prima facie* principles, and both Anglo-American and European principlism theories use as a fundament four principles. However, although the first principle is identical in both principlistic approaches, the names of the other three differ. We should consider those principles in the two approaches to see whether the nuances are or could be explainable.

The Anglo-American principlism defines the following four principles [6]:

1. Autonomy
2. Beneficence
3. Non-maleficence
4. Justice

It is not our purpose here to explain or comment the significance of these principles; there are several papers dealing with analyses and/or criticism of the theory [see for example refs. 7-12].

For the European principlism the stipulated four principles are [13, 14]:

1. Autonomy
2. Dignity
3. Integrity
4. Vulnerability

Our concern here is to analyze if the two principlistic approaches are clearly differentiable, if they are conflicting in an explainable manner, or if they are intertwined and convergent, therefore making the duality of the principlistic approach unnecessary. Firstly, in both Anglo-American and European concepts of principlism the principle of autonomy is recognized from a Kantian perspective, considering the human being as an end-in-itself. There is no contradiction here! Concerning the other principles, a brief analysis would suggest that within the principle of beneficence, human dignity is respected. On the other hand, by following the principle of non-maleficence, human integrity is protected in terms of both the integrity of the person performing the action and that of the person targeted by it. Finally, anyone can assert that real justice has to take care of people's vulnerability (including that of the poor – in terms of social analysis, or the vulnerability of sick people and their caregivers – due to their despair). Moreover, the four principles in any of the two principlism concepts become effective by a plethora of subsumed rules and norms. I may encourage the readers to try any kind of analysis on any of those rules and they will easily find intertwinements and convergences which create a real ethical network in the principlism usage within applied ethics.

Considering the swift analysis above, I believe an effort is necessary to wisely combine the two principlistic concepts even though the resulting one were grounded on a total of five principles: autonomy, dignity, integrity, vulnerability and justice. A putative critic, claimed by the fact that principles of beneficence and non-maleficence spring in the Hippocratic Oath, could be overcome by commentaries like the ones above, but leded more profoundly.

We should now focus on the basic aspects of utilitarianism. The concept belongs to the broader moral theory of consequentialism. The utilitarian moral philosophers think in terms of consequences, switching from the ethical notions of right and wrong to the non-ethical ones of good and bad. The utilitarian ethicists perceive as being moral those actions, judgments or decisions that are considered to be good, in the sense of producing happiness or well-being [15, 16]. The target of the utilitarian bioethicists is to maximize the good and minimize the bad of any act, judgment or decision [17].

It is easy to observe that the utilitarian view on morality is accountable for at least two principles of the Anglo-American concept: beneficence and non-maleficence. Consequently, it is difficult to find contradictions between the utilitarian maximization of the good and the principle of beneficence. It is similar if trying to analyze the relationship between the utilitarian minimization of the bad and the principle of non-maleficence. However, for a significant period of time there were contradictions between principlism and utilitarianism because the latter considered the human being as the only subject for impartial consideration in ethical analysis and decisions. The huge development of biomedicine and the complexity of the ethical issues raised by that progress determined the utilitarian bioethicists to widen their concern spectrum and to increase: *(i)* the variety of consequence types, *(ii)* the meaning of good and bad, *(iii)* the stakeholders considered as worthy recipients of impartial consideration, and *(iv)* the solutions for the maximization of the good and the minimization of the bad [15]. Therefore, the convergences between principlism and utilitarianism became more and more evident and the two concepts have to be considered simultaneously in ethical analyses and decisions. The applied ethics proved that neither principlism nor utilitarianism are sufficient for analyzing an ethical issue in biomedicine and for making a rational decision [15, 18].

In conclusion, whichever method is used during an ethical decision-making process, both principlism and utilitarianism have to be considered, and it is unreasonable to ignore any of them [19].

Ethical issues in translational medicine

In my opinion, a global approach concerning ethical issues in translational medicine is unproductive due to the great complexity of the field. That is why I will divide my commentaries by considering individually three of the research areas subsumed to this new field of biomedical research, which seem to be most sensitive to ethical issues and which also have raised the most extensive debates.

Ethical considerations on gene therapy

Gene therapy is generally defined as an action targeting insertion, correction or removal of a specific gene in a cell or a type of cell in order to treat a disease. The specific intervention could be done on either germ line cells or somatic cells.

The second approach needs taking care of the ethical rules regarding studies on human subjects, developed by most medical codes in bioethics. More sensitive in terms of ethics is the first approach, which should trigger a real ethical debate.

Broadly speaking, gene therapy is destined to correct a mutation producing a disability or threatening the life of a person. Despite the progress registered by our knowledge in the field of genetics and gene handling in biomedical research, very few steps in clinical application of those developments were taken. Therefore, the risks remain highly challenging and translational medicine needs to manage those uncertainties. This task is even more difficult as there are two unfortunate experiments to be found in the gene therapy clinical application history [3, 4]. Several questions could be formulated:

1. How far can we push the limits in defining the acceptable risks?
2. How could we define an authentic informed consent in the field?
3. How can we define the border between gene therapy and genetic enhancement?

The debate in search of an answer to the first question would highlight the fact that the acceptable risks in gene therapy treatment of lethal mutations are different from those acceptable in the case of non-lethal mutations. Moreover, it would also prove more ethical to support the efforts to develop research and to find solutions for treating diseases induced by lethal mutations. However, that is not a totally moral decision according to principlism, although it could be encouraged by utilitarianism. Therefore, it is ethical to develop research in any gene therapy direction, but we have to take care of the risks when deciding about clinical application. Research is needed even for a better knowledge of the cellular and molecular mechanisms targeted by the putative clinical applications and this progress will reduce the risks, will increase our ability to control and modulate the biological events and will increase the chances to obtain medical achievements.

The answer to the second question became essential in the context of the informational revolution in our times. The access to information corroborated with the vulnerability of the sick and that of their caregivers could easily result in vain hopes. Is it moral for the professionals to discourage people in accepting risky clinical interventions? Can such kind of discouraging action be part of the informed consent procedure? These new questions together with the third one listed above represent truly challenging ethical issues in need of serious debate.

Ethical approaches in tissue engineering

Tissue engineering is dealing with the *ex vivo* creation of living tissues or parts of organs in order to obtain final biological products compatible with the recipient's body needing them. This objective is a very complex one in both medical terms and from an ethical point of view [20-23]. Beside the debate about the ethical *versus*

non-ethical issues raised by the *ex vivo* creation of tissues or parts of organs [21] other aspects concerning the types of organ tissues needed to be tissue engineered could also be challenging. Is it necessary to make efforts in doing live body parts for those that could be successfully and effectively replaced by artificial devices (such as hands or legs)? This is a question with a difficult answer, especially if the analysis is done in terms of phenomenology. That means that even if principlism and utilitarianism are carefully considered, the final ethical decision is not necessarily the most rational one.

Again, in the tissue engineering research area, despite many promising results, the clinical application remains difficult to be accomplished. In this context, the first two questions listed under the previous subsection are also applicable to this area. On the other hand, some of the area-specific ethical challenges could involve the following [24, 25]:

1. Special risks induced mainly by the fact that a started intervention attracts irreversible processes that could follow a right pathway for repair or an unexpected wrong one;
2. Questionable benefits not only because of uncertainties mentioned under point 1, but also considering the level of the needed costs;
3. Cost reflections on the principle of justice (the access to clinical procedures is limited by those costs);
4. The putative donors of the samples for both research and clinical tests could be subjects of exploitation.
5. Finally, problematic issues appear when mixing human with animal materials due to cultural and religious beliefs and customs.

All the above-listed ethical issues lead to the conclusion that careful, well-informed debates are required. These have to involve every stakeholder (professionals, patients, caregivers, civil society representatives, politicians, research policy decision-makers, entrepreneurs etc.) in order to achieve the best and most rational ethical decision.

Ethical concerns in cell therapy

More than any other research area in translational medicine, cell therapy seems to be the most controversial one in terms of ethics. Cell therapy roughly means correction, repair or regeneration of diseased tissues by a transplantation of functional cells. Ethical debates in cell therapy became critical in the case of stem cell usage, because mature functional cell utilization draws ethical concerns more or less similar to those existing in the other research areas of translational medicine (source of the cells in the case of allogeneic transplantation, cultural and/or religious apprehensions toward xenotransplantation, risks etc.).

To date, three types of stem cells are theoretically available for cell therapy: embryonic stem cells, adult stem cells and induced pluripotent stem cells. As to the ethical debate, the most controversial issue remains the usage of embryonic stem cells [26-29]. The controversy based on the obtaining of embryonic stem cells for research and/or therapy has triggered professional, cultural and religious reactions. The most debated issues are about defining the personhood of an embryo and the act of killing [26, 30]. Perhaps in this moment it is really difficult to reach a rational ethical conclusion to these matters. In the future, the expected advancements in our knowledge of embryology and in the stem cell research development will allow us to find solutions to the ethical challenges of the cell therapy area. Fortunately, the controversies of this debate were accompanied by the efforts of the research scientists to find alternative sources for stem cells [31-33]. Despite the fact that the alternative sources for stem cells do not obviate the need for embryonic stem cells [34], they are being helpful in cell therapy research by allowing advancements in the stem cell biology and by overcoming many of the ethical issues. However, the results obtained when using stem cells in alternative sources still have to be confirmed by studies on embryonic stem cells. At least for this kind of control experiments human embryonic stem cells are very much needed as we speak. Therefore, both the ethical debate and the efforts to reach rational decisions represent a fundamental goal.

Beside the above considerations, as for the other two research areas mentioned earlier, the risks involved by the clinical application of the results obtained in cell therapy research development raise real problems both in terms of medical practice and ethics.

Principlism or utilitarianism in translational medicine ethical decision-making

Any ethical debate is helpful if ended with the adoption of a final decision or, at least, a recommendation to be considered and respected. In the context of our topic the question to arise would be the following: "What does the decision-making process have to consider: principlism or utilitarianism?" We should remember that in translational medicine one inevitable concern is the risk factor, and I suggest searching for an answer to the above-mentioned question by analyzing the risk threats. No activity is risk-free. The problem consists in knowing what acceptable level of risk there is behind one act or another. This problem should represent the main goal of the present analysis: to find out what is the acceptable risk in one area of translational medicine or another, in one clinical act or another. Could this level of acceptable risk be determined by following principlism or utilitarianism exigencies? Risks mean precautions elicited by the respect of autonomy, dignity, integrity, and vulnerability. Risks mean putative violations of the principles of beneficence, non-maleficence and justice. These last putative violations also come in contradiction with the objectives of utilitarianism. Therefore, a superficial analysis of the risk threats in translational medicine is enough to suggest that a rational ethical decision

must consider both principlism and utilitarianism, no matter what decision-making method is being used. That further suggests not only that a unified principlism concept would be helpful, but also that one concept unifying principlism and utilitarianism needs to be elaborated. This unified concept or framework could be entitled utilitarian principlism (similar to the unified theory created by John Edmund Hare and named “utilitarian Kantianism”). Moreover, the ubiquitous presence of the risk factor in every area of translational medicine justifies the idea of upgrading the precautions from the status of simple rules to that of principles.

Other questions regarding ethical decision-making in translational medicine could target the stakeholders responsible for the analysis, recommendations and/or decisions. Does an ethical decision in translational medicine have to be the result of a professional or a wide social debate? Could the civil society be a referee or a stakeholder in ethical decision-making in translational medicine? These questions are righteous due to the current information revolution and to the development of science and technology, which increases people’s expectations of the power of medicine, expectations that put enormous pressure on scientists, clinicians, research- and health-policy makers, and on the entrepreneurs.

In my opinion, all these categories of people, together with other appropriate representatives of the civil society are eligible as stakeholders in the process of ethical decision-making. That might prove to be an impediment in the process of ethical decision making, but through a wise management policy and a multiple-level approach of the process it would turn out to be a rational and acceptable end.

Concluding remarks

Making an ethical decision in any area of translational medicine is a difficult task and it seems to be even more difficult than in other fields, due to the medical and ethical complexity of this new biomedical research direction.

Any ethical decision regarding the challenging issues of translational medicine must consider a large number of stakeholders and needs a wise management of very clearly defined procedures in order to finalize the decision-making process in a reasonable amount of time, which is far from being an easy thing to do.

However, no matter how big the difficulties, translational medicine needs good and rational decisions destined to ensure patients’ protection and to allow the advancement of science and technology, which would finally lead to the progress and development of human society as a whole.

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