

Features of ethical expertise in planning and conducting clinical research in regenerative medicine

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Abstract

Nowadays we are dealing with a new level of biomedical science, that is «regenerative medicine», which provides opportunities for new treatments and the prolongation of human life. It demands that new evaluative criteria, both ethic and regulatory should be worked out and the society, scientific institutions and local authorities should respond in a quick and adequate way.

The authors, who are working in the frame of Megagrant Project of the Russian Government on creating Research, Education and Clinical Center of Regenerative Medicine, consider that one of the major tasks is regenerative medicine approaches to be governed by precise ethical guidelines, and social and cultural aspects. So, the first target of this collaboration is to define regulations and address ethical issues governing the field of bioengineered organs and tissues (simple or complex), both in the field of research and clinic. They present information about clinical application of tissue engineering in the world together with the summary of experience how regulations and authorities in Europe involving regenerative medicine approaches for Human Subjects. The authors presented the list of ethical rules for scientific research and clinical application in the field of regenerative medicine.

Key words: *regenerative medicine, evaluative criteria, ethical guidelines, scientific research, clinical application.*

Introduction

The achievements of scientific and technology progress in biomedicine have not only broaden its possibilities, but also influenced the traditional notion about good and evil, benefits of a patient, beginning and end of human life, and alongside contributed for the development of bioethics. Nowadays, we are dealing with a new medical science, that is regenerative medicine (RM). It is an emerging interdisciplinary field of research and clinical applications focused on the repair,

replacement or regeneration of cells, tissues or organs to restore impaired function resulting from any cause, including congenital defects, disease, trauma and ageing. It uses a combination of several approaches that moves beyond traditional transplantation and replacement therapies. These include, but are not limited to, the use of soluble molecules, gene therapy, stem cells transplantation, tissue engineering, and the reprogramming of cell and tissue types.

There are numerous ethical challenges raised by using bioengineer simple or complex tissues and organs and the use, inside or outside the body, of functioning autologous or xenogeneic cells. The pressure to advance this technique, driven by demand, the race for prestige, and the potential for huge profits, requires an early commitment be made to demonstrating the safety of various strategies in the laboratory and in animal models, and strict regulations. It demands that new evaluative criteria, both ethic and regulatory, should be worked out and the society, scientific institutions and local authorities should respond in a quick and adequate way to regulate this advances and respond to the ethical demands.

It's not a secret that the problem of commercial use of cell technologies has arisen quite often though it cannot be put up with initial clinical trials, when the ratio benefit/adverse side effects has not yet been studied sufficiently. The discussions about commercializing cell technologies with human embryonic stem cell may serve as an example. Non-controlled tourism that aims at stem cell therapy has become frightening legal business. One of the reasons for such chaos is that there are no "scientific" reports from the procedures, but there are some "market reports" where stem cell therapy has been substituted by the universal term "regenerative medicine".

Mass media representatives sometimes have no idea about new possibilities of the therapy. No state regulations exist so far or, if they do, they still can not solve the problem. This is the result of the 20-year development of regenerative medicine, as reported by Chris Mason and Elisa Manzotti in Science Magazine (1).

1. Bioethics. Lessons from the history

Bioethics (Greek *bios*, life; *ethos*, behavior) is the study of controversial ethics brought about by advances in biology and medicine. Bioethicists are concerned with the ethical questions that arise in the relationships among life sciences, biotechnology, medicine, politics, law, and philosophy. The term was coined in 1927 by Fritz Jahr, who "anticipated many of the arguments and discussions now current in biological research involving animals" in an article about the "Bioethical imperative," as he called it, regarding the scientific use of animals and plants.

The field of bioethics has addressed a broad swath of human inquiry, ranging from debates over the boundaries of life (e.g. abortion, euthanasia), allocation of scarce health care resources (e.g. organ donation, health care rationing), right to turn down medical care for religious or cultural reasons, ethical evaluation related to the

morality of medical treatments or technological innovations, and the timing of medical treatment of humans.

However, with improved technology and medical advances, it has become clear that a fundamental bioethical question: would it be ethical to deprive critically ill patients of the newest methods of treatment because their safety hasn't been proved? Modern history of protecting patients, involved in clinical trials, derived from the Nuremberg Code. Some principles of the Code are still considered to be basic while conducting human trials nowadays. For example, Article 1 of the Code considers patients' voluntary consent to clinical trials. Later on, Nuremberg Code recommendations have been developed in World Association of Doctors' Declarations: recommendations for the doctors conducting biomedical trials in humans. The 1st international ethical standard for conducting scientific researches in humans was published in the Declaration of the World Medical Assembling (WMA) (Helsinki, 1964) and the WMA Declaration of 2000 (Helsinki) is a worldwide recognized standard for conducting scientific researches in humans. The declaration was based on the principle of patients' individuality and the demand for independent ethical scientific projects expertise, especially created by research ethics committees which follow interdisciplinary approach in their work.

The history of biometrical research development is closely connected with improving the work of ethics committees as social bodies of control. There is worldwide a multilevel system of ethics control, and in Russia as well, while in foreign countries it is represented by different social, state and international organizations such as United Nations Educational, Scientific and Cultural Organization (UNESCO), World Health Organizations, European Council and Food and Drug Administration (FDA).

The Russian system of ethic control includes hospital ethics committees, medical institutions of higher education, scientific and research organizations and professional units of doctors, nurses and pharmacists. There is the Ethics Committee of the Ministry of Health Care and Social Development specially created to control the trials of new medicines and medical equipment. Another Ethics Committee (EC) was organized by the Russian Academy of Medical Science. The role of the committees is to guarantee observance of the rights, safety and health of all the real and potential participants of the research.

The peculiarity of the EC is the membership of the public, connected with different groups, aiming at protecting patients' rights, as well as of religious groups and lawyers. The role of the public in the development of bioethics is reflected in a number of legislative statements, for example: the European Council Convention "On Defending Human Rights and Dignity" while applying the achievements of Biology and Medicine: Convention on Human Rights and Biomedicine (1996) (previously called Convention on Bioethics). Article 28 of the Convention reflects the specificity of bioethical way of thinking: "Parties must become sure that fundamental problems connected with the progress in Biology and Medicine (socio-economic, ethic and legislative aspects, in particular)" should be widely discussed and become the concern of proper consultations.

2. Regenerative medicine: bioethics requirements

Recent advances have provided a real opportunity of giving life (artificial impregnation) to humanity, determining and modifying its qualitative characteristics (gene engineering, transsexual surgery), and prolongation life time (transplantation technologies: insulin therapy in patients with diabetes including insulin pumps, hemodialysis and hemofiltration in kidney pathology, transplantation of organs, cell therapy).

Obtaining cells from adults, umbilical blood and placental tissue raises ethical concerns (*Table 1*). Using human embryo as a source material for obtaining stem cells is a violation of the first principal of the WMA Declaration on therapeutic abortion adopted in 1983: the basic principal of a doctor is the respect for human life from the moment of conception. Another problem related to embryo cell therapy is the high risk of degenerative or tumoral transformation. Until the risk of tumor growth is not eliminated completely, it is not ethically justified to recommend this method to patients.

In the USA well-known President Decree introduced the limitations on the work with ESC, obtained after August, 9, 2001. Only those cell lines that had been received before this date could be used for federal fundamental investigations. Barack Obama's Administration removed all the limits concerning the work with such cells and supported stem cells researches by financing, especially in those spheres where cell technologies give the critical patients the chance to survive (severe impairments of spinal column, cancer, diabetes, Alzheimer's and Parkinson diseases). However, the confrontation is still ongoing. The recent resolution of Royce C. Lamberth, the Chief judge of the Federal Neighboring Court, runs as follows: "the state support of SCE contradicts the American legislation that does not allow spending money of tax-payers on experiments that can destroy or impair human embryos." The court stopped new procedures of stem cell researches financing, approved by B. Obama in spring 2009. Further development of hundreds of scientific researches almost stopped. In order to inform the society about the researches and the dangers of non-controlled cell therapy, the International Society for Stem Cell Research has been set up and is working actively.

Interestingly, the development of regenerative medicine does not only open new possibilities for treatment of a number of diseases, but also helps to reduce the tension of ethical problems. Regenerative medicine solves this problem by using self-cells for their differentiation into specialized cells of organs and tissues which are not functioning. These cell types are usually used to seed specific designed scaffold for manufacturing of artificial tissues and organs with suitable *in vivo* properties. In this connection, transplantation of donor organs may be reduced or become unnecessary, fully solving any histocompatibility issue and therefore the

need of immunosuppressive therapy, avoidance of its side effects, increase life expectancy as well as ethical problems.

Regenerative medicine represents a new approach, a new paradigm in treatment of human diseases, and include cell therapy and tissue engineering (application of scaffolds or matrices to grow new tissues or organs from isolated cells, tissue or synthetic compounds). Stem cell-based therapy (cell therapy) and its combination with natural or synthetic scaffolds to replace organs and tissues have been established as a clinical standard of care for conditions, such as haematopoietic SC transplants for leukaemia and epithelial SC-based treatments for burns and corneal disorders, and could be the alternative to tissue and organ transplantation. However, its clinical application demands strict ethical, legal and juridical regulations.

At present, several studies have been conducted in the fields of tissue transplantation (*Table 2*). The approaches may be based on simple tissue containing only one type of cells (cartilages, skin), tubular (vessels, urethra) and hollow tissue (trachea) as well as hollow organs (bladder, uterus). Ten years have passed since the bladder transplantation was performed. However, scientists still have difficulties to obtain the structure and cellular environment for more complex and three-dimensional organs, such as heart and lungs, and near regenerate and restore pancreas B-cells function in patients with insulin-dependent diabetes (type I).

We recently performed the first fully-tissue engineered complex tissue (windpipe) transplantation using a human decellularized donor trachea (characterized by structural and mechanical properties similar to native trachea, lack of immunogenicity, and containing pro-angiogenic factors) (2). A 7 cm long human decellularized trachea, seeded with autologous epithelial respiratory cells and mesenchymal stem cell-derived chondrocytes *via* a bioreactor, was successfully implanted to replace patient's left main bronchus (stenosed from tuberculosis). Today the patient is well, active with normal lung function and, more importantly, does not require immunosuppressive drugs. The method has then been improved, basing on the concept of the *in vivo* tissue engineering approach. The improved procedure involves:

- (i) scaffold: decellularized human trachea;
- (ii) cells: graft colonization is performed intraoperatively using autologous bone marrow MSCs for the external and epithelial cells (taken from the tracheal or nasal epithelial biopsies) for the internal tracheal surface, completely avoiding *in vitro* cell culturing, and using the patient's own body as a "living" bioreactor;
- (iii) factors: just before implantation, tracheal construct is intraoperatively conditioned with growing, differentiation and 'boosting' factors.

So far 9 patients have been transplanted using this *in vivo* tissue engineered approach. These transplantations have been performed in different European countries like Spain, UK, Italy, and Sweden respecting the respective ethical

issues and regulatory authority (*Table 3*). One of them has also been made in a young patient from Kazakhstan in the Russian Centre of Surgery named after B.V. Petrovsky (Russian Academy of Medical Sciences). Such experience of working in different countries pushes us to unification of ethical expertise and regulation. At the moment we are trying to do this in the frame of European Airways Institute which includes research and educational institutes of Sweden, Italy, UK and Russia.

To date, the new *in vivo* engineered transplanted tracheas are able to support themselves and have proved to possess a good epithelial coating, immediate vascularization and, upon all, a constantly wide open lumen for air passage. The positive results obtained suggested that starting from *in vivo* seeded bone marrow stem cells and using the body of the recipient patient as a biological, natural bioreactor, the *in vivo* tissue engineering approach may facilitate tracheal reconstruction and regeneration.

All the above reported researches are extremely encouraging, and it is expected that the collaboration between Prof. Macchiarini and the scientists of the Kuban State Medical University opens up new prospects for the development of regenerative technologies in Russia. However, to do so, one of our major tasks is that regenerative medicine approaches must be governed by precise ethical guidelines, and social and cultural aspects. For this reason, a recently obtained grant of the Government of the Russian Federation will definitively address and define bioethics and regulations of all aspect of regenerative medicine so that it can be used to support research project implemented by the leading scientists in Russian institutions of higher education, and clinicians.

One of the first target of this collaboration is to define regulations and address ethical issues governing the field of bioengineered organs and tissues (simple or complex), both in the field of research and clinic (*Table 4*).

Ethical Expertise in Russia

In 1993 such an independent branch, as Legislation of the citizens' health protection, presented by turn in a number of laws – “On transplantation of the human organs and/or tissues”, “On psychiatric support” etc. - was included into the General legal classifier of the RF legislation branches for the first time. It was stipulated by the political will for attaining the level of accordance with the international law principles and the WHO standards. The Russian Legislation of the citizens' health protection is an attempt to organize the work of the native health service in a liberal paradigm of right and legality being new for Russia, but having been proven by the western culture.

The ethical issues in medicine, including regenerative medicine, are being controlled at present by the following documents: *the Resolution of the Ministry of health care and social development of the Russian Federation of August, 31, 2010. No. 774N «On ethics board», the Federal law of May, 20, 2002 No. 54-FZ “On temporary prohibition of human cloning” (adopted by State Duma of the Russian Federation of 19.04.2002) and the Federal Law “On introduction of changes” in article 1 of the Federal Law “On temporary prohibition of human cloning” and at alias.*

The scientific-research organizations of the Ministry of health care and social development of Russia, Russian Academy of Medical Sciences, Russian Academy of Sciences and Federal Medical-Biological Agency carry out investigations in developing suitable approaches for cellular and genetic therapy in treating oncologic (lymphoma, myeloma, leukemia), and autoimmune (multiple sclerosis, lupus, rheumatoid arthritis, sclerodermatitis, Crohn's disease), diseases sickle-cell anemia, immunodeficiency states, cornea damages, apoplexy, infarction, Parkinson's disease, stomach and duodenum ulcers, spinal cord traumas, hepatic insufficiency . Investigations in the field of organ development based on cell technologies have also been initiated. The normative basis for developing and introducing biomedical cell technologies is absent. The procedure of developing and using biomedical cell technologies is regulated indirectly range of documents, some of which have not status of national law.

The Institutional Review Board on consideration of scientific researches in the field of cell technology development and its introduction in applied health care was created by the *Resolution of the Ministry No. 345 of August, 29, 2001*. The Institutional Review Board worked out “The temporary instruction on the order of investigations in the field of cell technologies and their use in public health institutions”. According to this instruction, “... using of human embryo cells must be limited by experimental models in vitro and in vivo on animals”. Using of hemopoietic stem cells is allowed, but approval for performing the 3rd stage of clinical research is the prerogative of the Ministry of health care and social development of the Russian Federation – the Institutional Review Board and the Ethics Committee. To get the permission to expand clinical therapy it is necessary

to present the results of clinical approbation of this method to the Ministry. Clinical approbation takes place in the research work of major scientific institutions on a small number of patients and is approved by the Academic Council of the institution and the Local Ethics Committee.

On May, 29, 2002 Specialized Program “New cell technologies for medicine” was approved at the session of the Russian Academy of Medical Sciences Presidium.

Currently the Ministry of health care and social development of the Russian Federation has brought up the project of the federal law “On biomedical cell technologies” for discussion. Debates on this project gave rise to stormy discussions and discordance of medical community opinions.

From our point of view, the following issues are required for the further development of this field of medicine:

- 1) improving the legislative basis;
- 2) creating stem cell banks equipped according to the GTP rules ;
- 3) training the specialists and improving the resource base of the clinics, as far as storing and using the stem cells is a very complicated technological process;
- 4) working out clear pro- and contra-indications for the stem cells usage.

Standard procedures for pre clinical and clinical trails in bioengineering and their ethics expertise

Obtaining new data on disease pathogenesis, the development of new diagnostic methods, safe and effective therapy demand conducting biomedical trials in humans, while the experiments must be done in animals.

Scientific value of the clinical findings must be counterbalanced by the observation of the ethics standards that aim at preserving safety for patients in trials. According to the data given above, present cell technologies are not clinically founded. However, the development of standards for conducting pre-clinical and clinical investigations and their use in practice is necessary and will help to meet the criteria of evidence based medicine and ethics.

The law project “On Medical Cell Technologies”, which is being discussed, demands to solve the problems of organization of pre-clinical and clinical investigations and their ethics ground. The stages in conducting the investigations and the scheme of expert evaluation are similar to those applied in clinical trials of medicinal substances. In fact, some cell technologies will soon become one of the innovated medicinal approach for patients. However, the first stage in the development of such medicine, as modulation and molecular making, is not controlled by state organizations. This is a very difficult scientific research and it does not show favorable results in 99% of cases. Financial aspects of the research project must also be considered. Scientists show concern for the financial aspects of the research project as it can lead to the reduction in the number of investigations in this new field of research.

It must be stressed that the experiments in healthy volunteers (1st stage) are not carried out and the groups of patients are not numerous. In addition, any investigation starts with the documents which are signed by the patients, thus written informed consent is obtained from each patient (*Table 5*). The patient's participation in the study as well as the written informed consent are confidential in accordance with the Russian and world ethics and the legislation of the RF.

On the contrary, biotechnologies must be transparent to the investigators in this field of scientific research, society and the State. It will prohibit concealment of unwanted events and the patient must be ready to accept these terms. At the same time, the standards must be corrected in accordance with the peculiarities of the regenerative medicine. The insurance item should also be considered.

Patients who undergo treatment with cell technologies are affected by serious diseases with very unfavorable prognosis. New technologies give them hope - such as the technology for creating bioengineered trachea and its transplantation to critically airway patients or to patients with burns of trachea and esophagus which will be developed in the Kuban State Medical University in the frame of this Megagrant Project.

Regenerative technologies are very expensive, so universities and scientific research institutes cannot pay insurance fee which is mentioned in the project. Only large commercial organizations can afford it. It should be noted that critically ill patients will use this opportunity to improve their relatives' welfare. It does not concern such fields of medicine as cosmetology or obstetrics in case nothing threatens the patient's life. The project must consider this difference.

Moreover in the period when the world begins to work, according to the principles of transmission medicine, prolonged periods of cell technology registration (210 days) will not be able to provide their rapid application in practice, and the patients will not get necessary help. Creating the balance between the observance of rights and main freedoms and the necessity to provide free research is an absolute advantage of the law nowadays.

Taking into consideration the gained experience in bioethics as well as personal experience, the authors tried to generalize bioethics principles in the field of biomedical cell technologies:

1. The lesson of ethically challenging pressures exerted on promising techniques, such as gene therapy, is a stark reminder of the ethical scaffolding that must be in place for bioengineering efforts particularly when there are so many potential patients and their doctors desperate for any remedy that might offer hope.

2. Those working on bioengineering organs must insist that clinical trials proceed only when there is sufficient evidence of safety and efficacy in hand. The willingness of dying and desperate patients to be involved in innovative organ bioengineering experiments is no substitute for the competency of investigators, the adequacy of the experimental infrastructure, full independent review of studies, or the ability to monitor subjects and publicly report on results.

3. Research teams must be prepared to demonstrate sufficient experience with cell, organ and tissue transplantation to confidently undertake these efforts.

4. Transparency about the techniques involved, cell sources, costs to be born by subjects, strategies for dealing with experimental failure, and the ability to assist subjects post treatment are ethically mandatory.

5. Minimizing conflicts of interest requires that when possible those with equity or financial interests in new techniques not be involved directly with testing or evaluating success

6. Further, given the complexity and enthusiasm likely to be associated with novel efforts to bioengineer organs and complex tissues, IRBs and research ethics committees must insist that steps to insure verified informed consent are in place and that study endpoints, recruitment strategies, plans for dealing with experimental failure, and managing conflict of interest are clearly described and fully disclosed to potential subjects.

7. The strongest ethical duty the bioengineering community faces is laying out criteria for what constitutes sufficient evidence of success to demarcate the evolution of an intervention from research to therapy.

Terminology

Medical ethics (*medical deontology*) - *the branch of ethics dealing with interrelations of healthcare professionals with patients and colleagues.*

Medical ethics - *ethical principles that healthcare professionals must follow. Medical ethics imposes certain obligations on a doctor to a patient as well as to other doctors. (The ecology of human. Term Dictionary. – Rostov-on-Don. B.B. Prokhorov. 2005).*

Bioethics (*derived from Greek βίος – life, ἠθική – ethics, science of morality*) – *science of morality of human activity in medicine and biology. The first mentioning of the term in medical journal is dated to 1971. In Encyclopedia of Bioethics (Vol. 1, p. XXI), bioethics is defined as “systematic study of moral characteristics - including moral evaluation, decisions, behavior, guidelines etc. – of achievements in biological and medical sciences.”*

Ethics committee – *the structure conducting ethical expertise. Ethics committee must depend neither on researchers, whose project undergoes examination, nor on science or medical institution, where the research ought to take place. The approval of Ethics committee is obligatory for conducting the research.*

Biomedical cellular technology – *the process of getting cell product for renewal of structures and functions of human tissues and organs through cell substitution or through activation of the human body reducing processes, for creating tissues and organs with bioengineering methods (tissue engineering) and its subsequent use in medical activity as well as for targeted drug deliver(9).*

Cell product – *the product consisting of cell lines and adjuvants or of cell lines, adjuvants combined with pharmaceutical substances and/or medical devices (combined cell product) received as the result of biomedical cellular technology.*

Cell therapy – *biomedical technology based on the use of stem cells or stem cell products.*

Regenerative medicine – creating living functioning tissue for “mending” or replacing tissue or organ which was damaged or lost its capacity as the result of aging, malady or impairment.

*** The article is supported by the Government of the Russian Federation in the frame of research projects implemented under the supervision of leading scientists at Russian institutions of higher education(№ 11.G34.31.0065)**

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Supplements

Table 1. Potential pros and cons of the different cell types to be used in translational regenerative medicine

Characteristics	Stem cells	iPSCs	Progenitor cells
Ethical issues	Embryonic SCs ++ Adult SCs -	disputable	No ethical issues
Self-renewal <i>in vivo</i>	Unlimited	Unlimited	Limited
Self-renewal <i>in vitro</i>	Unlimited	Unlimited	Limited
Maintenance of self-renewal	Yes	Likely Yes	No
Potentiality	Pluripotent/ Multipotent	Pluripotent	Usually unipotent, sometimes oligopotent
Population	Reaches maximum numbers of cells before differentiation	Not determined	Does not reach maximal population
Significant risk of teratoma	SC type dependent risk	Significant risk	No teratoma risk

++ serious; - no or marginal ethical issues; SCs (stem cells) MHC (major histocompatibility complex); iPSCs (induced pluripotent stem cells)

Table 2. Clinical application

Target Organ	Donor sources & Decellularization Method	Seeded cell type	Source
Trachea ¹	<i>Human donor trachea</i> - DNase and Deoxycholate	- Autologous MSCs and epithelial cells	2008, Barcelona (Spain), 30-year-old woman
Tracheal patch ²	<i>Pigs Jejunum</i> - Mechanical removal, sodium acid solution, DNase, Desoxycholate	- Autologous fibroblasts and muscle cells	2003, Hannover (Germany), 58-year-old man
Bladder ³	<i>Acellular scaffolds</i>	Autologous urothelial and muscle cells	2000-2005, Winston-Salem (USA), 4 to 19-year-old children
Vessel (portal vein) ⁴	<i>Human donor portal vein</i>	Not published	2011, Göteborg (Sweden), 10-year-old child
Aortic root ⁵	<i>Human donor aortic root</i> – hypotonic solution, acids and cryopreservation	unseeded	2002-2003, Rochester (USA), 31 to 80-year-old patients
Heart valve ⁶	<i>Human pulmonary heart valve</i> – Trypsin/EDTA	Autologous endothelial progenitor cells	2002, Chisinau (Moldova), 11 and 13-year-old children
Dermis and Hernia ⁷	<i>Human Dermis</i>	Mostly unseeded	Baltimore 2000-2005

Table 3. Regulations and Authorities (Europe) involving regenerative medicine approaches for Human Subjects

Treatment	Ethical approval from local committee - IRB	Medical Product Agency (MPA) Approval of Trial	GMP (manufacturing permit for clinical trial issued by MPA)	GMP (hospital exemption permit issued by MPA)
Clinical trial of a medicinal product	X	X	X	-
ATMP exploratory treatment (few patients) - Hospital Exemption	X	-	-	X
Vital Indication (life saving intervention)	X/(X)	-	-	-

Table 4. Ethical rules for researcher

Research:

- Ethics is central to scientific integrity;
- Ethics review is automatic for studies which include the use of cells and/or use of non-human primates.
- Research undertaken in developing or emerging countries should comply with the highest ethical standards;
- Animals are important in research but this should not contravene fundamental animal rights and respect;
- Consider the impact of the research in terms of scientific advancements (publications, patents *etc.*) but also and mainly in terms of human dignity and social and cultural impact;
- Adopting always the maximal transparency about the involved techniques, with involvement of local and national the Ethical Committees, national health, education and scientific authorities, advisory boards, and patients;
- No authorization should be granted to perform clinical studies in the field of regenerative medicine without having peer-reviewed safety and efficacy preclinical data;

Clinical Trials:

- Ethics review is automatic for studies which include a research intervention on human beings, and/or the use of human;
- Informed Consent: inform the patients with clear and uncomplicated language, detailing the procedure, the benefits and possible foreseeable discomforts/adverse risks;
- Only persons able to freely understand and question should consent. Vulnerable persons (prisoners, mentally ill, children) are excluded, although their participation in studies can be accommodated if they benefit directly. In such cases, obtaining informed consent requires special attention and involves the next of kin or legal and medical representatives.
- Transparency about strategies for dealing with experimental failure, and the ability to assist subjects post treatment is ethically mandatory.
- Create advanced training programs to teach and share the ability to reproduce the techniques.
- Those with equity or financial interests in new regenerative medicine techniques should not be involved directly with testing or evaluating success. This minimizes conflict of interest.
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Table 5. Informed Consent should include:

<ul style="list-style-type: none"> • Informed consent is not confined to medical research, it applies to all human participation in research;
<ul style="list-style-type: none"> • Each participant in a research project, prior to consent, should be clearly informed of its goals, its possible adverse events and the possibility to refuse to enter or to retract without adverse consequences, and any procedure that is experimental;
<ul style="list-style-type: none"> • A description of the foreseeable risks or discomforts that are reasonably expected;
<ul style="list-style-type: none"> • A description of any benefits to the subject or to others which are reasonably expected;
<ul style="list-style-type: none"> • A disclosure of any appropriate procedures that might be advantageous;
<ul style="list-style-type: none"> • A statement describing the extent to which confidentiality of records identifying the subject will be maintained;
<ul style="list-style-type: none"> • For research involving more than minimal risk, an explanation as to whether there are any treatments or compensation if injury occurs and if so what they consist of or where further information can be obtained;
<ul style="list-style-type: none"> • Identify the contact person for answers to questions about the research and research subject's rights, and whom to contact in the event of injury to the subject;
<ul style="list-style-type: none"> • A statement that participation is voluntary, withdrawal from the research can be undertaken at any time without loss of benefits which the subject is otherwise entitled to

The above applies to the use of human tissues too