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The Origins and Evolution of Bioethics

Bioethics was officially baptized in 1972, but its birth took place a decade or so before that date. Since its birth, what is known today as bioethics has undergone a complex conceptual metamorphosis. This essay loosely divides that metamorphosis into three stages: an educational, an ethical, and a global stage. In the educational era, bioethics focused on a perceived "dehumanization" of medicine by the rising power of science and technology. Remedies were sought by introducing humanities, ethics, and human "values" into the medical curriculum. Ethics was one among the humanistic disciplines, but not the dominant one. In the second era, ethics assumed a dominant role as ever more complex dilemmas emerged from the rapid pace of biological research. As such dilemmas were applied to medical practice, the need for a more rigorous and more formal analysis of their moral status was clear. Philosophically-trained ethicists had an obvious role. They began to teach, write, and profoundly influence medical education and practice. In the third – and present – period, the breadth of problems has become so broad that ethicists must, themselves, draw on disciplines well beyond their expertise – e.g., law, religion, anthropology, economics, political science, psychology, and the like. The era of bioethics as a global enterprise is upon us. The original hope for humanizing medicine has not been overtly successful; however, much has been accomplished of value to patients, the profession, and society. Medical morality has been transformed into a formal, systematic study of a whole range of issues of the greatest significance to humanity. Now the major challenge is one of identity, or inter-relationships and connections between the theoretical and the practical. Bioethics has outgrown its beginnings. [2]

Prof. Edmund Pellegrino MD (1920 - 2013)

Texts taken from: [2] Pellegrino E. The Origins and Evolution of Bioethics: Some Personal Reflections. *Kennedy Inst. Ethics J*, 1999, 9(1): 73-88.

PÔVODNÉ PRÁCE

ORIGINAL PAPERS

CLASSIFICATION AND ETHICAL ISSUES REGARDING ADVANCED THERAPY MEDICINAL PRODUCTS

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1. Introduction

Advanced therapy medicinal products (ATMPs), which include gene and cell therapy and tissue engineered products, represent a new category of medicines in the EU law. *„Advanced therapy medicinal product"* designation does not exist as a legal categorization elsewhere in the world, and therefore a specific regulatory framework has been created for these medicines which took effect on December 30, 2008.

Such a designation was a consequence of rapid advances in life sciences using human biological materials. The novelty, complexity, and technical specificity of the application of these advances into medical practice created significant regulatory issues at EU level since a number of cell therapies and engineered tissues have been introduced in some Member States during the last decade. First of all, these novel therapies with high complexity need to be addressed quite differently from traditional pharmaceuticals or biologicals in their development, manufacturing, or administration process [1]: from establishing batch consistency, product stability to product safety and efficacy through pre-clinical, clinical studies and marketing authorization. Secondly, despite the fact that novel therapies generate huge healthcare expectations and constitute an alternative therapeutic strategy to conventional clinical therapy, for which no effective cure was previously available, at the same time they are expected to bear a higher risk potential than other biological medicinal products [2] not foreseen for transplantation materials such as tumorigenicity, cell (de)differentiation, and patient integration [3]. Thirdly, the novel therapies were subject to different legal regimes: gene therapy, for example, genetic immunotherapy for cancer, and cell therapy, for example, articular chondrocytes for cartilage repair, already had been regulated as medicinal products [4] under the Community legal framework since 2003 [5] while tissue-engineered products, for example, skin replacement materials, remained largely unregulated by EU legislation. And finally, a specifically tailored and harmonized regulatory framework was necessary to meet these challenges and to *"ensure the free movement of these medicines within the European Union (EU), to facilitate their access to the EU market, and to foster the competitiveness of European pharmaceutical companies in the field, while guaranteeing the highest level of health protection for patient"* [6].

Several possibilities were considered for regulatory framework harmonization [7]: to extend the scope of Directive 93/42/EEC on medical devices [8]; to propose a separate regulation based on principles of "*new approach*", to set up a specific regulatory framework based on a semi-centralized procedure, to establish a mechanism in which the European Union and the Member States would share the responsibility of granting marketing authorizations. Instead of creating a legal framework designed only for tissue engineered products, the European Commission chose a more global and integrated *"advanced therapies approach"*, built on already-existing legislation, in particular regulation 726/2004/EC [9], directives 93/42/EEC on medical devices, 2001/83/EC on the Community code relating to medicinal products for human use [10] and 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (so called Tissue and cells directive) [11].

A consolidated regulatory framework for these innovative treatments was finally introduced by a *lex specialis* - Regulation 1394/2007/EC of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation 726/2004/EC (ATMP Regulation) [12]. The Regulation provides tailored regulatory principles for the evaluation and authorization of these innovative medicines, filled a pre-existing regulatory gap between gene and cell therapies and engineered tissues for therapeutic purposes by subjecting the latter to the general EU pharmaceutical legislation. At the same time *lex specialis* alongside with the setting of uniform manufacturing, quality and pharmacovigilance standards to protect human health established a regulatory framework for newly created class of medicines – *"advanced therapy medicinal products"* which is more stringent than the one applied to conventional medicinal products [13]: unlike directives such as a Directive 2001/83/ on the Community code relating to medicinal products for human use which are binding only for result, a Regulation is binding in its entirety and directly applicable. For example, the ATMP Regulation extends to ATMPs the centralized EU procedure for marketing authorization [14] through the European Medicines Agency (EMA) [15]. Licensing requirements for ATMPs to a large extent are the same as for biological medicines, however the regulatory regime for ATMPs is especially focused on safety requirements, for example, market authorisation review by special committee established within EMA, additional data regarding safety, efficiency and quality is required, post-authorization requirements such as traceability and pharmacovigilance which requires efficacy follow-up and, etc.

2. Classification of Advanced Therapy Medicinal Products

ATMP regulatory framework applies to *"products"* which correspond to the EU legal definitions and *„which are intended to be placed on the market in Member States and are either prepared industrially or manufactured by a method involving an industrial process"* [16]. EU law does not provide a direct definition of ATMP, instead of it the ATMP Regulation defines, more or less, what does and does not constitute such a product. It indicates a short list of defined medicinal products for human use which fall within a category of ATMPs [17]: gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products (SCTMPs) and tissue engineered products (TEPs). Combined ATMPs which incorporate medical devices or active implantable devices form a subtype of ATMPs, keeping in mind the fact that devices are regulated by substantially different regime under EU law. These product groups share similar characteristics and bear a similar risk potential. In reality, the designation of the three mentioned therapeutic classes and their combination with medical devices into a group of biological medicinal products represents the current state of the art in medicinal products field.

However, ATMP Regulation also leaves open questions about the effective regulation of certain classes of medicinal artifacts, which may fall outside the EU regime, whether in the absence of a specific legislative norm or by the discretion power conferred by law to committees of selected specialists (in our case the Committee for Advanced Therapies (CAT) of EMA [18]) which consider innovations on a case-by-case basis and thus deciding the regulatory route [19].

2.1. Gene Therapy Medicinal Products mean a biological medicinal products which fulfill the following two conditions that have both to be fulfilled simultaneously: a) contain an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence; b) therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence [20]. A product which may fall within the definition of a somatic cell therapy medicinal product or a tissue engineered product, and a gene therapy medicinal product is considered as a gene therapy medicinal product. [21] From these definitions follows that GMO-containing medicines saved they fulfill above mentioned conditions may fall within the category of GTMP. In this case an applicant for a market authorization for a GMO-containing GTMP shall submit to EMA assessment of the potential risk of the said product to the environment [22]. Gene therapy vaccines against infectious diseases are excluded from the definition. [23]

2.2. Somatic Cell Therapy Medicinal Product means a biological medicinal product which fulfils the following two conditions: a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor (so called non-homologous use); b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues. [24]

The first condition includes two options: cells either should be substantially manipulated (1) or designated for non-homologous use (2).

Taking into account the methodological complexity of the SCTMPs the Art. 2 (1) (c) of ATMP Regulation provides with a negative definition of substantial manipulation. It refers to the list (Annex I) which specifies what *"in particular"* should not be considered as a substantial manipulation. These include cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation [25], cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, and vitrification. Vice versa, examples of substantial manipulations may vary and include among others cell expansion (culture), genetic modification of cells, differentiation with growth factors, etc.

It is interesting to note that the language of the Art. 2 (1) (c) phrased in somewhat general terms suggests that the list is non-exhaustive. This leads the Committee for Advanced Therapies (CAT) of EMA to give itself the power based on scientific considerations to "*consider any other manipulation as "non substantial"* [26]. As an example, CAT cites the radiolabelling of leukocytes. According to CAT, this technique, which has been used in clinical practice in a hospital setting since many years, and which has no significant impact on the biological properties of the cells, should not be considered a substantial manipulation [27].

The concept of *"non-substantial manipulation"* is closely inter-related with *"homologous use"* of cells. It happens to be one of the confusing points in the ATMP field, because non-homologous use of cells or tissues by definition makes them an ATMP. Non-homologous use means that cells or tissues (substantially manipulated or not) are not intended to be used for the same essential function or functions in the recipient as in the donor: for example, autologous bone-marrow derived cells which are only minimally manipulated (e.g. bone-marrow aspirate) but injected in the patient's heart for regeneration of the myocardium. Vice versa, hematopoietic stem cells either autologous or allogeneic for transplantation purposes do not fall under the ATMP remit, unless they are substantially manipulated and/or used for non-homologous use [28].

SCTMPs (the same could be said about tissue engineered products) differs significantly in their risk regarding safety, quality and efficacy: for example, it is acknowledged that products based on autologous cells or tissues such as cartilage transplants represent much lower risk than their allogeneic counterparts. However, the legislation does not address such distinctions and as a consequence the development of certain products bears unnecessary stringent regulatory requirements which directly translate into higher costs and limited patients' access. For example, during public consultation attention has been paid to the fact that in Belgium the reimbursement price of autologous chondrocyte cultures which were classified as ATMPs and obtained centralized marketing authorization is ten times higher than that of non-ATMP classified autologous chondrocyte cultures [29].

2.3. Tissue Engineered Product according to Article 2(1)(b) of ATMP Regulation 1394/2007/EC means a product that (a) *"contains or consists of engineered cells or tissues"*, and (b) *"is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue"*. The Regulation admits that the origin of cells/tissues may be human or animal, or such TEPs may represent both types. The composition of TEPs could be more complex:*"[t]he cells or tissues may be viable or non-viable", "[i]t may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices"*. From the definition of TEP are excluded products *"containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action."* Additionally, as in the case of SCTMPs, TEPs should meet one of requirement indicated by Article 2(1)(b) of ATMP Regulation: substantial manipulation or non-homologous use of cells or tissues.

In this context, the *"mode of action of the product"* is particularly important in order to ascertain whether the product is for treatment, prevention or diagnosis of a disease, and exerts its activity via a pharmacological, immunological or metabolic action or whether the mode of action of the product is regeneration, repair or replacement of cells/tissues. In the former case the mode of action will determine the classification of the product as SCTMP, in the latter case – as TEP. The ascertainment of mode of action should be based either on data and/or on current scientific knowledge [30]. In case of uncertainty, the CAT may only classify that a product is an ATMP, and the rest conclusion is based on the provision of ATMP regulation: a product which may fall within the definition of a TEP and within the definition of a SCTMP is considered as a TEP (Art. 2 (4)).

2.4. Combined ATMP means an advanced therapy medicinal product that fulfills the following conditions: it must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC [31] or one or more active implantable medical devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC [32], and its cellular or tissue part must contain viable cells or tissues, or its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to (Art. 2 (d) of ATMP Regulation). A medical device or an active implantable medical device should meet the essential requirements described in Directive 93/42/EEC concerning medical devices and Direc-

tive 90/385/EEC relating to active implantable medical devices, to ensure an appropriate level of quality and safety. Both directives were amended by Directive 2007/47/EC [33].

3. Some Ethical Issues regarding Advanced Therapy Medicinal Products

Debate on ethical issues has been one of the most conspicuous features of the EU-level negotiation of the ATMP Regulation. From the beginning the position of EU institutions was that the EU is not supposed to harmonize divergent ethical standards. The European Commission requested to prepare a report on the ethical aspects of the regulation in preparation from the European Group on Ethics of new technologies [34]. The published report identifies a number of ethical issues including informed consent, commercialization of body parts, privacy protection, and use of embryonic stem cells. Ethical controversies which resulted in the delay of the adoption of the ATMP Regulation are not addressed in the Regulation as these were considered to fall under the national competence. Due to broadness of this problematic field, we will limit ourselves and only consider several issues which are closely related to the classification of ATMPs.

3.1. Embryonic cell-based products. Ethical controversies regarding human embryonic stem cell research and eventual development of medicinal products on the base of such research sparked during the legislation process of ATMP Regulation at the European Parliament. The approach of European Commission was to avoid the sensitive debate on the use of human embryonic stem cells which already took place during the adoption of so called Tissue and cells directive. In contrast, European Parliament proposed an amendment which would explicitly exclude ATMP that *"contain or are derived from human embryonic and foetal cells, primordial germ cells and cells derived from those cells"*. The proposal was rejected by the European Commission and the Council. The rationale [35] according to them is that ethical provisions proposed by the European Parliament *"fall outside the scope of Article 152 [of the Treaty] that provides for public health protection and not the implementation of ethical objectives as such"*. However, in order to reflect the fact that among Member States there are divergent views on the moral legitimacy of the use of human embryos for research and therapeutic purposes in the final draft it was agreed, that the Regulation *"should not interfere with decisions made by Member States on whether to allow the use of any specific type of human cells, such as embryonic stem cells, or animal cells" (Preamble (7))*. Nevertheless the regulatory status of ATMPs that contain or are derived from human embryonic cells remains uncertain: which authorization procedure - centtralized or national – should these products follow? In a trust-based environment it would be reasonably to consider, that by default such procedure should be national. Keeping in mind the current state of the research in the field [36], products using these materials are unlikely to be introduced into the market in foreseeable future. However, it seems that no treaty or statutory provision precludes centralized marketing authorization of embryo cell based therapies as such. Once marketing authorization is obtained, the principle of free movement of goods is applied to such products. Can a Member State invoke a public morality exception (Art. 36 of the Treaty) [37] to a free movement of centrally authorized medicinal product? In theory the answer could be positive, but here the exception may be challenged by other competing principles of EU law. The final say in this case would belong to the Court of Justice of European Union who is in charge of interpretation of EU law.

3.2. Xenogeneic cell-based products. The principal objective of such treatment is reconstitution of human cell/tissue/organ functions. EU legislative discussions over ethical aspects of xenotransplantation or transplantation of living cells, tissues or organs from animals to humans were no less fierce, especially regarding authorization of products derived from human-animal hybrids or chimeras. Less opposition met transplantation of somatic animal cells or tissues to the human body for therapeutic purposes [38]. The proposal of European Parliament to ban any authorization of products derived from human-animal hybrids or chimeras or containing tissues or cells originating or derived from human-animal hybrids or chimeras received the same fate as in case of embryo derived products. At the same time the Regulation recognized that it should not interfere with decisions made by Member States on whether to allow the use of animal cells. However, regarding the use of animal cells or tissues for ATMPs the Regulation is more specific: it indicates that "*[a] tissue engineered product may contain cells or tissues of human or animal origin, or both"* (Art. 2(1)). Accordingly, xenogeneric origin of cells is approved by relevant legislation of SCTMPs [39].

Xenogeneic cell-based therapy could be administered in two ways: (a) through implantation/ infusion into a human recipient or (b) through extracorporeal treatment when animal cells are brought into contact with human body fluids, tissues or organs [40]. It offers a potential treatment for end-stage organ failure, but at the same time it also raises significant unique medical issues: risks of transmitting known and unknown pathogens of animal origin, risk of introducing new infectious diseases into the general population through adaptation in an immuno-suppressed host, the risk of immunological rejection of animal cells/tissues, etc. [41] Despite of the acknowledged uniqueness of such risks, European Commission published Detailed guidelines on good clinical practice specific to advanced therapy medicinal products [42] where such risks were not specifically addressed: clinical trials of cell and tissue-based products whether allogeneic or xenogeneic are considered indistinctively. The part of the problem rests in the heart of ATMP Regulation which enlists only very few classes of ATMPs. However, current developments in the field raise the necessity of articulation of distinct category of novel medicines in the ATMP regulation [43]. An instructive example can be learned from the United States where regulatory authorities prefer to keep xenotransplants normatively separated from cell- and tissue-based therapies. Whenever animal cells makes part of cell- or tissue based product or even in case when animal cell lines are used for culturing (so called feeder layers) [44] more stringent rules on product safety are applied. In this regard the Center for Biologics Evaluation and Research within FDA, which regulates biological products for human use, both investigational and licensed, considers that *"[i]f a feeder cell line of animal origin is used to propagate human cells (i.e., human and non-human animal cells are co-cultivated), the final product falls within the definition of a xenotransplantation product"* [45].

Much of the same could be said about the use of cells, tissue or genes from transgenic animals. The Directive 2001/83/EC or ATMP Regulation do not describe in precisely clear manner the source of the biological material for ATMPs and consequently the distinction between cells or tissues of conventional animals and transgenic animals (and human-animal hybrids or chimeras!) is not addressed. This could lead to two regulatory scenarios. On the one hand, development of products derived from transgenic animals would be subject to ATMP regime only in case if transgenic modification is directly related to the therapeutic, prophylactic or diagnostic effect. On the other hand, if cells or tissues are not substantially modified or their "*essential*" function differs in donor and recipient, such products fall outside the ATMPs regulation even if they may bear risks as high as ATMPs.

3.3. Products that modify the germ line genetic identity of human beings. Germ line gene therapy involving the genetic modification of germ line cells (for example, in the early

zygote) and introducing genetic changes into early embryos which become incorporated into all cells of the body and, as such, are passed on to future generations, is considered to be entirely different. The idea of such gene therapy has elicited considerable ethical, scientific, and political controversy. For example, it raises an important ethical concern such as its possible use for eugenics. During the discussions on Commission's proposal for ATMP Regulation European Parliament proposed to exclude from the scope of the Regulation "products modifying the germ line genetic identity of human beings" along with the products derived from human-animal hybrids or chimeras [46]. The Parliament referred to the *Articles 1 and 13 of the Oviedo Convention which unambiguously make it clear, that human dignity is compromised when the inheritance of genetic identity is altered.* The Art. 13 of the latter [47] explicitly prohibits any intervention seeking to modify the human genome of any descendants. *Moreover, such products are neither properly subject to clinical trials under Clinical trials directive 2001/20/EC [48] nor legally patentable under Biotechnology directive 98/44/EC* [49.] *In the opinion of parliamentarians as a matter of legal consistency these products should not be eligible for authorization under the Regulation. By way of exception, it was proposed that the said exclusion should not be applied to products intended to treat cancers of the gonads.* This proposal was successfully countered by a "patients' need" concern which was endorsed in the final draft of the Regulation, resulting in the removal of all "ethical amendments". However, as in case of embryo-derived products the regulatory status of products modifying the germ line genetic identity remains unclear and even contradictory. It is clear that such products do not fit SCTMPs definition, but they can be considered as GTMPs since additional genetic information is introduced for which the definition applies. But the main issue concerns legal incoherency: even if such products theoretically fall within the scope of ATMP Regulation, their clinical development is outlawed by Clinical trials directive which makes them impossible to reach authorization stage. Moreover, 17 Member States have ratified Oviedo Convention and therefore a ban on the genetic modification in germ line is incorporated into the national legislation of these countries. The fact of inconsistency is acknowledged but at the same time the legal reality from the point of view of international law seems to be ignored in the Proposal for a Regulation on clinical trials on medicinal products for human use which repeals Clinical trial directive [50]. The proposal eliminates the existing ban and thus opens the possibility to access EU market for such highly contested "products". It seems that European legislator is quite selective when it "takes into account" ethical-legal principles of Oviedo Convention (Preamble (8) of ATMP Regulation): for example, such principles enshrined in Oviedo Convention or in its Protocols as voluntary and unpaid donation or anonymity of both donor and recipient, altruism of the donor and solidarity between donor and recipient were welcomed in the Regulation.

3.4 Vaccines against infectious diseases. Another important issue concerns vaccines against infectious diseases which have been explicitly excluded from the ATMP definition. This vaccine exemption was introduced into the Commissions Directive 2009/120/EC, amending Directive 2001/83/EC on the Community code relating to medicinal products for human use [51]. In reality, for example, live recombinant viral vectors (delivering genes encoding specific antigen sequences into human somatic cells) could fulfill the definition of GTMP when administered for example in oncology, but similar products would not be classified GTMPs when intended as prophylactic or therapeutic against infectious disease, based on this legal exemption [52]. From scientific point of view the reason why this class of biologicals unlike their counterparts was excluded from stricter regulatory regime is unclear: if a prophylactic vaccine contains the same active substances and is produced in the same or similar way as other GTMPs, the requirements applied for these medicinal products should be the same as those for GTMPs.

There seems to be other reasons of different nature such as concerns for public health policy. It is acknowledged that in a context of abundant and even conflicting messages about benefits and safety of vaccines in the in new or social media uninformed perceptions may lead certain population groups to question the benefits of vaccination, or foster the public to be more worried about alleged adverse effects of a vaccine than about the disease itself [53]. Accordingly, the dominant negative public opinion on gene technology in the EU might have a negative impact on the vaccines classified as a GTMP [54] If that presupposition is correct, it could be argued whether the explicit exemption will comply with the objective of ATMPs regulation that any rules governing their production, distribution and use must to safeguard public health. The exemption of prophylactic vaccines does not mean that they escape rigorous regime: for example, according the Annex of the Regulation (EC) No 726/2004 such products as products developed by the use of recombinant DNA technology, products employing controlled expression of genes coding for biologically active proteins in prokaryotes or eukaryotes including mammalian cells, products prepared by hybridoma or monoclonal antibody methods or products for the treatment of special diseases such as for cancer and viral diseases were already subject to marketing authorization centralized procedure. However, these vaccines are subject to the general regulatory regime for biological products which is less strict than the one for ATMPs, for example, in terms of additional data regarding safety, efficiency and quality or post-authorization requirements. Here seems that an effective science communication, science education of the society and better two-way dialogue between developers and society could be more suitable instruments to address specific problems of public health policy.

4. Conclusions

One of the main objectives of the ATMPs regulatory regime is to guarantee the highest level of health protection for patient through minimizing risks which may bear these innovative products. In this respect ATMPs are grouped into classes which share similar characteristics and bear a similar risk potential. However, even within a product class certain products may differ in their risk while regulatory requirements remain the same for all products: for example, autologous cell-based products have much less safety concerns unlike allogeneic or xenogeneic products. ATMP Regulation also leaves open questions about the effective regulation of certain classes of medicinal artifacts, which may fall outside the EU regime and thus compromise Community commitments in the field of free movement of medicinal products while guaranteeing appropriate protection to patients against risks. These regulatory gaps to a significant extent are related to EU reluctance to deal with ethically controversial issues in the legislation. Such therapies as embryonic cell-based products, germline modification or xenotransplantation at their current state of the art bear more risk than benefit. It would be reasonable to suggest that EU legislator should adopt more tailored risk-based medicinal product classification which would address a broader spectrum of issues.

Notes and References

[1] The Committee for Advanced Therapies (CAT) and the CAT Scientific Secretariat. Challenges with advanced therapy medicinal products and how to meet them. *Nat. Rev. Drug Discov.* 9 (2010), 195–202. **[2]** Schneider, C.K., Celis, P. Opinion: Challenges with advanced therapy medicinal products and how to meet them. *Nat Rev Drug Discov.* 9 (2010), 195-201. **[3]** The Committee for Advanced Therapies (CAT) and the CAT Scientific Secretariat. Chal-

lenges with advanced therapy medicinal products and how to meet them. *Nat Re. Drug Discov.* 9 (2010), 195–202. **[4]** A "medicinal product" is defined as: *"Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis."* See Article 1 § 2 and Annex I of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, OJ L 311, 28.11.2001, pp. 67-128; as amended by Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, OJ L136, 30.04.2004, pp. 34-57. **[5]** Directive 2003/63/EC of the Commission of 25 June 2003 amending directive 2001/83/EC, OJ L 159 of 27.06.2003, pp. 46-94. **[6]** European Medicines Agency. EU Regulation on advanced therapies. Accessed Oct. 13, 2013. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000295.jsp&mid=WC0b01ac058007f4bb **[7]** Mahalatchimy, A. Access to Advanced Therapy Medicinal Products in the EU: Where Do We Stand? *Eur J Health Law.* 18 (2011), 305-317. **[8]** Directive 93/42/EEC of the Council concerning medical devices, OJ L169, 12.07.1993, pp. 1-43. **[9]** Regulation 726/2004/EC of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ L 136, 30.04.2004, pp. 1-33. **[10]** Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use, OJ L311, 28.11.2001, pp. 67-128. Directive as amended by Commission Directive 2003/63/EC, OJ L159, 27.06.2003, pp. 46-94, and Directive 2004/27/EC, OJ L136, 30.04.2004, pp. 34-57. **[11]** Directive 2004/23/EC of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, OJ L102, 7.04.2004, pp. 48-58. **[12]** OJ L 324, pp. 121–137. **[13]** However, recently some authors expressed cautious concern about the stringency of ATMP regulatory framework: the first generation of ATMPs have already been in use for more than a decade, while the development of many new ATMPs is hampered by many limitations and challenges; see C.K. Schneider et al. Challenges with advanced therapy medicinal products and how to meet them. *Nat Rev Drug Discov*, 9 (2010), 195-201. **[14]** The centralized procedure allows applicants to obtain a marketing authorization that is valid throughout the EU, as well as in Iceland, Liechtenstein and Norway. It is compulsory for medicinal products manufactured using biotechnological processes, for orphan medicinal products and for human products containing a new active substance which was not authorized in the Community before 20 May 2004 (date of entry into force of Regulation 726/2004/EC) and which are intended for the treatment of AIDS, cancer, neurodegenerative disorder or diabetes. **[15]** The EMA is a technical agency acting as a central point of coordination of the existing scientific resources in the European Union for the regulatory and scientific evaluation of medicinal products both for human and veterinary use. The main tasks among others are regulatory and scientific contribution to the life cycle of medicinal products, harmonization of technical requirements for marketing authorization at EU and international level, support to the European Commission on policy matters relevant to medicinal products. See Regulation of the Council 2309/93/EEC of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products. OJ L 214. 1993; pp.1–21. **[16]** Regulation 1394/2007/EC Preamble (6) **[17]** Regulation 1394/2007/EC Art. 2 (1) (b) and (4). **[18]** The Committee for Advanced Therapies is the sixth Committee within the EMA. It was established in accordance with ATMP Regulation on to bring together the best available expertise on ATMPs. The CAT's main responsibilities are, among other things, to give advice on the classification of a given product whether it falls, on scientific grounds, within the definition of an ATMP and to evaluate ATMPs with regard to their quality, safety or efficacy. **[19]** The CAT like EMA is not a decision-making body and has an advisory function only. All decisions made under the regulation are made by the European Commission. However, keeping in mind rapid processes in the field of innovative medicine which are found not consistent with the timing of the legislative process, the European Commission gives itself the power to modify the ATMP regulation through comitology procedure; see Tallachini, M.Ch. Cellule e tessuti come terapie avanzate: una biopolitica europea. Rodota, S., P. Zatti (eds.) *Trattato di biodiritto. Il governo del corpo.* 2011. Milano: Giuffre Editore, pp.1063-85. To similar conclusions come A. Mahalatchimy et al. The European Medicines Agency: a public health European Agency? *Med Law.* 31 (2012), 25-42. **[20]** Directive 2001/83/EC Annex I Part IV as amended (implementing Directive 2009/120/EC) **[21]** Regulation 1394/2007/EC Art. 2(5). **[22]** Regulation (EC) 726/2004; EMA Guideline on scientific requirements for gene therapy medicinal products (EMEA/CHMP/GTWP/125491/2009). **[23]** Directive 2001/83/EC Annex I Part IV as amended (implementing Directive 2009/120/EC) **[24]** Directive 2001/83/EC Annex I Part IV as amended **[25]** From the scientific or clinical perspective it can be argued that cell irradiation can have a substantial effect on the biological characteristics and physiological functions that may be relevant also for the intended therapeutic application, see Ancans, J. Cell therapy medicinal product regulatory framework in Europe and its application for MSC-based therapy development. *Front Immunol.* 3 (2012), 253. **[26]** EMA, Reflection paper on classification of Advanced Therapy Medicinal Products (EMA/CAT/600280/2010) **[27]** Ibid. **[28]** Ibid. **[29]** EMA. Overview of comments received on "Reflection paper on classification of advanced therapy medicinal products (EMA/600280/2010), 7 December 2012" (EMA/CAT/658287/2012). **[30]** EMA, Reflection paper on classification of Advanced Therapy Medicinal Products (EMA/CAT/600280/2010) **[31]** Directive 93/42/EEC of the Council of 14 June 1993 concerning medical devices. OJ L 169, 12.07.1993, pp. 1-60. **[32]** Directive 90/385/EEC of the Council of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medicinal devices. OJ L 189, 20.07.1990,p p. 17-41. **[33]** Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007 Amending Council Directive 90/385/EEC on the Approximation of the Laws of the Member States Relating to Active Implantable Medical Devices, Council Directive 93/42/EEC Concerning Medical Devices and Directive 98/8/EC Concerning the Placing of Biocide Products on the Market. OJ L 247, 21.09.2007, pp. 21-55. **[34]** EGE. Report of the European Group on Ethics on the ethical aspects of human tissue engineered products, 29-06-2004. **[35]** This common position of the Commission and the Council reiterated the position expressed during the legislative process of the Tissue and cells directive, see Common Position adopted by the Council with a view to the adoption of a Directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, storage and distribution of human tissues and cells, 9 July 2003, 10133/03. **[36]** Stem cell research: hope and hype. *Lancet.* 365 (2005), 1904; Braude P., Minger S.L. and Warwick R.M. Stem cell therapy: hope or hype? BMJ. 330 (2005), 1159-1160. **[37]** Treaty on the functioning of the European Union. OJ C 83, 30.03.2010, pp. 47-199. Article 36 provides a list of justified prohibitions or restrictions on imports or/and exports of goods: necessity grounded on public morality, public policy or public security; the protection of health and life of humans, animals or plants; the protection of national treasures possessing artistic, historic or archaeological value; the protection of industrial and commercial property. **[38]** Report on the proposal for a Regulation of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation 726/2004/EC (COM(2005)0567 – C6-0401/2005 – 2005/0227(COD)), A6-0031/2007 final. **[39]** Directive 2001/83/EC, Annex I Part IV as amended. **[40]** EMA. Guideline on xenogeneic cell-based products. (EMEA/CHMP/CPWP/83508/2009) **[41]** Ibid. **[42]** European Commission, Enterprise and Industry Directorate-General. Detailed guidelines on good clinical practice specific to advanced therapy medicinal products. (ENTR/F/2/SF/dn D(2009) 35810) **[43]** Tallachini, M.Ch. Cellule e tessuti come terapie avanzate: una biopolitica europea. Rodota S., P.Zatti (eds.), *Trattato di biodiritto. Il governo del corpo.* 2011. Milano: Giuffre Editore, p.1063-85. **[44]** CAT currently considers cell expansion by culturing as a substantial manipulation. Although it may not necessarily lead to immediate changes in cell functionality or the phenotype of the cells before and after culture, it cannot be ruled out that the biological characteristics, physiological function(s) or structural properties of the cells are changed by cell culture, see EMA. Reflection paper on classification of Advanced Therapy Medicinal Products (EMA/CAT/600280/2010) **[45]** U.S. Department of Health and Human Services, FDA, CBER. Guidance for FDA Reviewers and Sponsors: Content and Review of

Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs), April 2008. **[46]** Explanatory statement, Revised Draft report 8.11.2006. **[47]** Council of Europe. Convention for the protection of human rights and the dignity of the human person with regard to the application of biology and medicine: Convention on human rights and biomedicine, Oviedo, 4 April 1997, ETS n. 164. **[48]** "No gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity", Article 9§6 of Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, OJ L121, 01/05/2001, pp. 34-44. **[49]** Article 6§2 (b) of the Directive 98/44/EC of the European Parliament and the Council of 6 July 1998 on the legal protection of biotechnological inventions, OJ L 213, 30.7.1998, pp. 13–21. **[50]** Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (COM(2012) 369 final). **[51]** Directive 2009/120/EC of the Commission of 14 September 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products, OJ L 242, 15.09.2009, pp. 3-12. **[52]** EMA. Reflection paper on classification of Advanced Therapy Medicinal Products (EMA/CAT/600280/2010). **[53]** ECDC technical document. Communication on immunization – building a trust. Stockholm: ECDC; 2012, p. 2. **[54]** Grunert, K.G. , Bredahl, L., Scholderer, J. Four questions on European consumers' attitudes toward the use of genetic modification in food production. *Innovative Food Science and Emerging Technologies.* 4 (2003), 435–445.

Juškevičius J.: Classification and Ethical Issues Regarding Advanced Therapy Medicinal Products./Problémy klasifikácie a etiky vo vzťahu k produktom pripraveným špičkovými technológiami. Med. Etika Bioet., Vol. 20, 2013, No. 3-4, p. 2 – 7.

Abstract

European Union's (EU) Regulation No. 1394/2007 has introduced a new regulatory category of medicines – advanced therapy medicinal products, into the EU legal system. They are divided at present into three major groups: gene therapy, somatic cell therapy and tissue engineered medicinal products. The reasons for such classification are complex and vary in a broad spectrum comprised from political-legislative to scientific concerns. The aim of the paper is to discuss some classification issues that arise from the reluctance of the European legislator to address in a clearer way some important ethical issues with regard to those advanced therapies.

Key words: advanced therapy medicinal products, classification, ethical issues

Abstrakt

Nariadenie Európskej únie (EÚ) č. 1394/2007 uviedlo do legislatívneho systému EÚ novú kategóriu liekov – produkty pripravené špičkovými technológiami. Rozdeľujú sa v súčasnosti do troch hlavných skupín: produkty na génovú terapiu, na terapiu somatickými kmeňovými bunkami, a produkty pripravené úpravou tkaniva. Príčiny tejto klasifikácie sú komplexné a zahŕňajú široké spektrum od politicko-legislatívnych až po vedecké dôvody. Cieľom príspevku je poukázať na niektoré problémy uvedenej klasifikácie, ktoré vznikajú v dôsledku neochoty európskeho zákonodarcu venovať väčšiu pozornosť etickým otázkam, ktoré prinášajú tieto nové terapeutické možnosti.

Kľúčové slová: produkty pripravené špičkovými technológiami, klasifikácia, etické otázky

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INTEGRATEDETHICS® PROGRAM AS AN EXAMPLE OF SYSTEMIC APPROACH TO ETHICAL ISSUES IN HEALTH CARE FACILITIES

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Introduction

The IntegratedEthics® (**IE**) program [11] is "a comprehensive approach to managing ethics in health care organizations. It represents a radical departure from the traditional ethics committee model. The goal of IE is the continuous improvement of ethics quality." It may be seen as a rather unique approach dealing with ethical issues and conflicts both at the level of individual ethics (solutions to issues concerning a particular clinical case), and at the level of a health care facility understood as a complex system providing medical care (systemic approach to 'ethical atmosphere' of a particular facility).

IE program was developed by the National Center for Ethics in Health Care of the United States Department of Veterans Affairs. The Center itself was founded in 1991 to promote better practices in the field of medical ethics in the health care facilities of the US Department of Veterans Affairs (VA). "From 2008, this program was implemented in all VA's medical centers", and it was one of the "Top 25 Programs" in the 2011 Innovations in American Government Award", and also by the U.S. Office of Government Ethics as a "Program Excellence and Innovation Award". [12]

IE program refers to a complex and diversified approach, concerned primarily with ethical problems solving in the daily health care, but, at the same time, providing very useful educational and assessment tools.

In this paper, we shall discuss the structure and implementation of IE program in dealing with the concrete ethical problems in VA health care facilities.

Ethics Consultation, Preventive Ethics and Ethical Leadership

Ethics Consultation, Preventive Ethics and Ethical Leadership are three key tools of the systemic approach of the IE program.

It aims not only at solutions finding in particular clinical ethics cases (ethics consultation), but also at improving the strategies of ethics implementation in a particular medical facility (preventive ethics). The main task of the ethical leadership as part of IE program is to support both previously mentioned tools, and to shield the need of a systemic ethics approach by the personal authority of the main persons in a healthcare facility.

This structure well resembles that of an iceberg. [2] The top of the iceberg represents the particular solution to a particular ethical issue of a particular case (ethics consultation). However, this solution is reached in a particular health facility with its own atmosphere and ways of solving particular issues. The main question on this level of ethical reflection is how to create structures, strategies and processes that could not only facilitate the ethics consultations, but also how to make them more transparent and systematically viewed. This is the main task of the so-called preventive ethics. And that is the underwater portion of the 'iceberg'. The water, in which the iceberg swims, is the main task for the ethical leadership. It means to shield

and cultivate the whole environment and 'organization's culture' of the health care facility.

Ethics Consultation

Ethics consultation within IE program is "a service provided by an individual ethics consultant, ethics consultation team, or ethics committee to help patients, providers, and other parties resolve ethical concerns in a health care settings." [3]

The goals of IE program ethics consultation are: [4]

- promoting practices consistent with high ethical standards,
- helping to foster consensus and resolve conflict in an atmosphere of respect,
- educating participants to handle current and future ethical concerns.

Three **models of ethics consultation** are used within IE program. Each of those posses both some advantages and disadvantages (**Figure 1**). [5]

Figure 1 Models of ethics consultation used within the IntegratedEthics® (IE) program

- ***Individual ethics consultant model***
  - advantages:
    - minimum logistical and time difficulties
    - able to react very quickly
  - disadvantages:
    - consultant must possess all required knowledge
    - minimal feedback about personal prejudices
- ***Ethics committee model***
  (ethics committee, typically 6 – 20 members)
  - advantage:
    - collective proficiency, diverse perspective and multidisciplinary approach
  - disadvantages:
    - time needed for logistics
    - not suited for quick responses
    - "group thinking"
    - a large group of professionals (may be intimidating for the patient or the family)
- ***Ethics consultation team model***
  (combines both models)
  - advantages:
    - several and diverse perspectives
    - flexibility
    - less intimidating for family and patient
  - disadvantages:
    - less efficient than the individual consultant model
    - fewer checks and balances than the committee model

The core competencies for health care ethics consultation were summarized by the American Society for Bioethics and Humanities in its report published in 1998. [1] IE program proceeds from these recommendations too. The report requires ethics consultants to posses three categories of **core competencies**: knowledge, skills, and character traits (**Figure 2**).

The key competence, obviously, is the ability to formulate and solve ethical problems in a particular case. To attain this, IE program offers an elaborated working method under the acronym name CASES. The constituent steps in solving a particular ethical problem by CASES method are summarized in **Figure 3**.

Figure 2 Core competencies of ethics consultants (According to [1].)

- Knowledge
  - moral theory, moral reasoning
  - ethical concepts and issues of medical practice
  - health care practice
  - cultural and religious issues
  - health care environment
  - health law
- Skills
  - identifying the nature of the case
  - analyzing ethical concerns
  - facilitate formal and informal meetings
  - demonstrating critical thinking
  - fostering a respectful, supportive environment for expression of moral views
- Character traits
  - humility
  - tolerance
  - self-knowledge
  - courage

Figure 3 Ethical problem solution by CASES method (According to [6].)

- C – Clarify the consultation request
  - characterize the type of consultation request
  - obtain preliminary information from the requester
  - establish realistic expectations about the consultation process
  - formulate the ethics question
- A – Assemble the relevant information
  - consider the types of information needed
  - identify the appropriate sources of information
  - gather information systematically from each source
  - summarize the case and the ethics question
- S – Synthesize the information
  - determine whether a formal meeting is needed
  - engage in ethical analysis
  - identify the ethically appropriate decision maker
  - facilitate moral deliberation about ethically justifiable options
- E – Explain the synthesis
  - communicate the synthesis to key participants
  - provide additional resources
  - document the consultation in the health record
  - document the consultation in consultation service records
- S – Support the consultation process
  - follow up with participants
  - evaluate the consultation
  - adjust the consultation process
  - identify underlying systems issues

Especially appreciable seems to be the way of putting ethical questions as noteworthy and beneficial. It has a very definite form [7]:

- *Given the uncertainty or conflict about values:* What decisions or actions are ethically justifiable?
- *Given the uncertainty or conflict about values:* Is it ethically justifiable to (*decision or action*)?

Preventive Ethics

According to IE program, preventive ethics is the 'underwater body of the iceberg'. It comprises the "activities performed by an individual or group on behalf of a health care organization to address systemic ethics issues." The main goal is to "improve health care quality by identifying, prioritizing, and addressing ethics quality gaps on a system level." [8]

Two **models for preventive ethics** activities are used [9]:

- **small team** – one or more "core" members (with a permanent role in preventive ethics),
- one or more ***ad hoc*** members (who have subject matter expertise relevant to the particular ethics issue that is being addressed).

The model of preventive ethics used depends on the organizational structure of the health care setting. The core competencies for preventive ethics activities are referred to as follows [9]:

- knowledge of quality improvement principles, methods, and practices,
- knowledge of relevant organizational environment(s),
- knowledge of organizational change strategies,
- knowledge of ethics topics and concepts,
- skill in moral reasoning,
- skill in systems thinking.

The method of preventive ethics implementation is abbreviated by acronym ISSUES. It is depicted in **Figure 4** [9].

Figure 4 The method of preventive ethics – ISSUES (According to [9].)

- I – Identify an issue
  - identify ethics issues proactively
  - characterize the type of issues
  - clarify each issue by listing the improvement goal
- S – Study the issues
  - diagram the process behind the relevant practice
  - gather specific data about best practices
  - gather specific data about current practices
  - refine the improvement goal to reflect the ethics quality gap
- S – Select a strategy
  - identify the major cause(s) of the ethics quality gap – do a root cause analysis
  - brainstorm about possible strategies to narrow the gap
  - choose one or more strategies to try
- U – Undertake a plan
  - plan how to carry out the strategy
  - plan hot to evaluate the strategy
  - execute the plan
- E – Evaluate and adjust
  - check the execution and the results
  - adjust as necessary
  - evaluate your issues process
- S – Sustain and spread
  - sustain the improvement
  - disseminate the improvement
  - continue monitoring

Ethical leadership

The ethical leadership is the third tool of IE program approach. It is the 'water in which the iceberg is immersed'. It is not as clearly structured as the previous ones and comprises "the activities on the part of leaders to foster an environment and culture that support ethical practices throughout the organization." [10] The main role of ethical leadership is "in creating, sustaining, and changing organization's culture through their [i.e. ethical leaders'] own behavior and through the programs and activities they support and praise or neglect and criticize." [10]

Leaders in the VA health care facilities have the following particular obligations [...][10]:

- As public servants, VA leaders are specifically responsible for maintaining the public trust, placing duty above self-interest, and managing resources responsibly.
- As health care providers, VA leaders have a fiduciary obligation to meet the health care needs of individual patients in the context of an equitable, safe, effective, accessible, and compassionate health care delivery system.
- As managers, leaders are responsible for creating a workplace culture based on integrity, accountability, fairness, and respect".

Ethical leadership is characterized by four unique features (with no acronym) given in the **Figure 5** [10].

Figure 5 The features of ethical leadership (According to [10].)

- D – Demonstrate that ethics is a priority
  - talk about ethics
  - prove that ethics matters to you
  - encourage discussion of ethical concerns
- C – Communicate clear expectation for ethical practice
  - recognize when expectation need to be clarified
  - be explicit, give examples, explain the underlying values
  - anticipate barriers to meeting your expectations
- P – Practice ethical decision making
  - identify decisions that raise ethical concerns
  - address ethical decisions systematically
  - explain your decisions
- S – Support your local ethics program
  - know what your ethics program is and what it does
  - champion the program
  - support participation by others

Comments and conclusions

IE program is a well elaborated and straight-forward approach to ethical issues encountered within the health care facility operations. It provides very useful tools for action not only at the individual level, but also at the systemic and leadership ones.

In Europe, different approaches of clinical ethics implementation into the daily healthcare practice have been tried. But few are as comprehensive and systematic as IE program. IE program good acceptance in the USA, however, does not guarantee it will be an equally successful, workable solution in the European context. IE program clearly helps in dealing with concrete ethical issues more systematically and precisely.

It would be necessary, e.g., to analyze its philosophical-anthropological basis, especially with regard to the ethics consultation. Is it "principlism" of Beauchamp and Childress? There is no clear link between the "principles" and the questions asked within the CASES approach. Other ways of analyzing and solving ethical issues are available as well (e.g. according to Jonsen's et all. publication *Cli-*

nical Ethics. A Practical Approach to Ethical Decisions in Clinical Medicine; ethics questionnaires developed at Bochum or Nijmegen universities are widely accepted in Germany).

The preventive ethics level may posses the same limits as the ethics consultation. Those are even more important, as the aim of preventive ethics is developing strategies of dealing with conflicting ethical situations in practice. The relationship between preventive ethics and ethics consultation is not yet defined clearly enough in actual IE program. E.g., preventive ethics approach, if exercised 'mechanically' might be found rather invasive to the freedom of personal conscience. Dealing with possible conscientious objections of the staff members is as yet not elaborated well enough in IE program.

The ethical leadership is the least clear tool of IE program. It has strong virtue ethics aspects with highly demanding requirements imposed on the 'ethical leaders'. This poses also as one of its limits. 'Ethics leaders' are expected to be virtuous persons. Such position of theirs could be easily shaken in the eyes of others by some necessary decisions (albeit ethically sound) that are not accepted easily by the people involved.

IE program is a very interesting approach in dealing with difficult ethical issues encountered in the health care facilities today. Its further study in comparison with other systems available in Europe and beyond is surely warranted. Especially with a view of defining a systemic approach that might best fit the local/regional situation in Czech Republic health care facilities, and/or health care centers in Central and Eastern Europe.

References

[1] Comp. Aulisio, Mark., P., Arnold, Robert, M., Youngner, Stuart, J., Ethics consultation. From Theory to Practice, The Johns Hopkins University Press, Baltimore : 2003, p. 165 – 209, ISBN 0-8018-7165-4. **[2]** Fox, Ellen, Berkowitz, Kenneth, A., Chanko, Barbara, L., Powel, Tia, EthicsConsultation [Abbreviation "EC"]. Responding to EthicsQuestions in Health Care, [Online]. [21/11/13]. Available at <http://www.ethics.va.gov/ECprimer.pdf>, p. 4, without ISBN. **[3]** Comp. EC, p. ii. **[4]** Comp. EC, p. 13. **[5]** Comp. EC, p. 14. **[6]** EC, p. 25. **[7]** Comp. EC, p. 31. **[8]** Fox, Ellen, Bottrell, Melissa, Foglia, Mary, Beth, Stoeckle, Rebecca, Preventive Ethics [Abbreviation "PE"]. Addressing Ethics Quality Gaps on a Systems Level, [Online]. [23/11/13]. Available at <http://www.ethics.va.gov/PEprimer.pdf >, p. ii, without ISBN **[9]** Comp. EP, iii. **[10]** Comp. Fox, Ellen, Crigger, Bette-Jane, Bottrell, Melissa, Bauck, Paul, EthicalLeadership [Abbreviation "EL"]. Fostering and EthicalEnvironment&Culture, [Online]. [23/11/13]. Available at <http://www.ethics.va.gov/ELprimer.pdf>, p. ii, without ISBN. **[11]** This article is based on information of the National Center for Ethics in Health Care of the United States Department of Veterans Affairs, accessed on websites related to the main website of National Center for Ethics in Health Care, [Online]. [25/11/13]. Available at <http://www.ethics.va.gov/index.asp>. **[12]** Comp. U.S. Department of Veterans Affairs, The Integrated Ethics Overview, [Online]. [25/11/13]. Available at <http://www.ethics.va.gov/the IntegratedEthics/index>.

Matějek, J.: IntegratedEthics® Program as an Example of Systemic Approach to Ethical Issues in Health Care Facilities./ Program IntegratedEthics® jako příklad systémového přístupu k řešení etických problémů ve zdravotnických zařízeních. Med. Etika Bioet., Vol. 20, 2013, No. 3-4, p. 7-10.

Abstract

The paper gives an overview of the IntegratedEthics® Program as a systemic approach to dealing with ethical issues encountered daily in the work of health care facilities. It was developed by the National Center for Ethics in Health Care of the United States Department of Veterans Affairs. The program, in addition to offering well structured consultations of individual cases ('ethics consultation'), also entails systemic implementation of ethics at the level of individual health care facilities ('preventive ethics'). An important role is also to be played by the 'ethical leadership' exercised by the health care facilities managers. The program may provide interesting inspirations for dealing with ethical problems in health care facilities outside USA, including those in (Central and Eastern) Europe.

Key words: IntegratedEthics® program, ethics consultation, preventive ethics, ethical leadership

Abstrakt

Článek podává přehled o programu IntegratedEthics®. Program IntegratedEthics® je systémovým přístupem k etickým otázkám, se kterými se každodenně setkávají pracovníci zdravotnických zařízení. Tento program vznikl v National Center for Ethics in Health Care of the United States Department of Veterans Affairs. Kromě toho, že tento program nabízí jasně strukturované vedení konzultací individuálních případů (složka ‚etické konzultace'), zahrnuje také systémovou implementaci etiky na úrovni zdravotnického zařízení samotného (složka 'preventivní etika'). Důležitou roli hraje také management těchto zařízení jako 'etické vedení' (angl. ethical leadership). Tento program může poskytnout zajímavou inspiraci k přístupům k etickým problémům ve zdravotnických zařízeních i mimo USA, včetně (střední a východní) Evropy.

Klíčová slova: IntegratedEthics® Program, etická konzultace, preventivní etika, etické vedení

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DOKUMENTY / DOCUMENTS

ETICKÉ ASPEKTY POVINNÉHO OČKOVANIA

Uznesenie č. 43/51 zo dňa 19.11.2013

Etická komisia Ministerstva zdravotníctva Slovenskej republiky

Etická komisia Ministerstva zdravotníctva Slovenskej republiky sa na svojich riadnych zasadnutiach dňa 1. októbra 2013 a dňa 19. novembra 2013 v Bratislave zaoberala niektorými etickými otázkami, ktoré sa objavujú vo verejnosti v súvislosti s aktuálnou diskusiou o národnom programe povinného očkovania. Táto diskusia bola v poslednom čase akcentovaná prebiehajúcim konaním pred Ústavným súdom Slovenskej republiky, ako aj narastajúcimi aktivitami zástancov i odporcov povinného očkovania vo verejnom priestore, osobitne v oblasti printových a elektronických masovokomunikačných prostriedkov a internetových sociálnych sietí.

Komisia pozorne zvažovala argumenty oboch strán a je si vedomá rizík spätých s realizáciou národného programu povinného očkovania. Súčasne však skúmala i argumenty v prospech zachovania systému národného programu povinného očkovania. Komisia sa preto rozhodla k etickým otázkam povinného očkovania prijať nasledovné stanovisko:

Realizácia národného programu povinného očkovania predstavuje **jeden z významných úspechov vývoja medicíny** a preventívnej zdravotnej starostlivosti na území Slovenskej republiky. Možno ho zároveň označiť ako jedno z dosiaľ najúčinnejších a najbezpečnejších opatrení zdravotnej starostlivosti, s neporovnateľne priaznivým pomerom účinnosti, medicínskeho prínosu (princíp *beneficiencie* – dobročinnosti) a bezpečnosti (princíp non-maleficiencie – neškodnosti). Aj vďaka tomu z povedomia širokej verejnosti takmer úplne vymizli obavy a strach spojené s ochoreniami, proti ktorým je tento národný program zameraný.

Komisia sa domnieva, že realizácia a výsledky národného programu povinného očkovania sú **v súlade s hodnotou verejného zdravia** a z etického hľadiska **v súlade aj so správne chápanými etickými princípmi** *spravodlivosti, solidarity, autonómie, transparentnosti a správneho spravovania* verejných záležitostí, ktoré patria k hlavným etickým princípom v oblasti medicíny a zdravotnej starostlivosti, s akceptáciou v celom súčasnom kultúrnom svete.

Účinnosť, bezpečnosť, alebo epidemiologická oprávnenosť národného očkovacieho programu nebola zatiaľ v rámci **odbornej diskusie** presvedčivo vyvrátená, skôr naopak. Veľká časť diskusie sa pritom presunula do oblasti médií a sociálnych sietí, kde ale neboli vždy zabezpečené podmienky pre kvalifikovanú diskusiu. Napriek tomu sa podarilo čiastočne ovplyvniť verejnú mienku. Komisia sa však pri svojich záveroch opierala o vedecky overené informácie, v rámci ktorých zvažovala pre i proti systému národného programu povinného očkovania na základe princípov „medicíny založenej na dôkazoch“ (angl. evidence – based medicine).

Komisia si uvedomuje, že v dlhej histórií úsilia o vývoj a zabezpečenie vakcín a vakcinačných programov sa vo svete vyskytli aj **viaceré zlyhania**, odborné omyly, či neetické konania zo strany príslušných inštitúcií, či samotných výrobcov vakcín. Komisia si je tiež vedomá, že nie všetky tieto poľutovaniahodné zlyhania boli dostatočne objasnené a odkomunikované širšej verejnosti, vrátane informácií o prijatých systémových opatreniach na zamedzenie ich opakovaného výskytu pri vývoji, klinickom skúšaní, či výrobe vakcín a pri realizácii vakcinačných programov.

Komisia si je plne vedomá **rizík a možných nežiaducich účinkov očkovaní**, ktoré sú súčasťou národného programu povinného očkovania. Ide najmä o neočakávané nežiaduce reakcie. Medicínskym aj etickým imperatívom musí byť rešpektovanie všetkých medicínskych kontraindikácií očkovania u daného dieťaťa, ako aj sledovanie výskytu, hlásenie a adekvátne riešenie nežiaducich účinkov vakcinácie. Súčasťou tohto úsilia lekárov, sestier a ďalších zdravotníckych pracovníkov je aj správna komunikácia a pochopenie pre rodičov očkovaných detí.

Komisia však zdôrazňuje, že ide o **riziká pomerne zriedkavé,** navyše, ich výskyt sa po nedávnom zrušení povinného plošného očkovania voči tuberkulóze ešte znížil. Komisia sa taktiež domnieva, že reálny pomer účinnosti, medicínskeho/zdravotného prínosu pre dieťa voči riziku daného očkovania je v súčasnosti najpriaznivejší zo všetkých účinných preventívnych opatrení zdravotnej starostlivosti.

Pre časť našej verejnosti predstavuje určitý morálny problém skutočnosť, že pri vývoji a výrobe niektorých očkovacích látok sa na pomnoženie a získanie vírusov, potrebných na ich prípravu, používajú stabilné bunkové kultúry, na ktorých získanie sa pred viacerými desaťročiami použili **tkanivá umelo potrateného ľudského plodu**. Tieto medzinárodne definované stabilné bunkové kultúry nie je v súčasnosti ľahké pri výrobe daných očkovacích látok nahradiť. Treba však upozorniť, že aktuálne vyrábané a používané vakcíny neobsahujú žiadne súčasti potratených ľudských embryí a plodov, ani sa tieto pri ich výrobe nepoužívajú – ako sa možno presvedčiť z príslušných medzinárodne definovaných a prísne kontrolovaných výrobných postupov. Komisia odporúča príslušným štátnym orgánom a inštitúciám, ako aj výrobcom očkovacích látok, aby sa na tieto skutočnosti bral primeraný ohľad pri rozhodovaní o vývoji, výrobe, zaobstaraní a financovaní očkovacích látok, osobitne očkovacích látok hradených z verejných finančných prostriedkov.

Komisia si je tiež vedomá, že povinné očkovanie môže predstavovať **zásah do osobnej integrity**, domnieva sa však, že ide o také obmedzenie základného práva, ktoré spĺňa účel a povinné očkovanie prispieva k lepšej ochrane a garancii základných spoločenských hodnôt, ako napr. verejné zdravie alebo ochrana práv iných.

Kvôli limitácii všetkých rizík spojených s problematikou očkovania vyzýva komisia všetkých zdravotníckych pracovníkov, osobitne pediatrov, sestry, lekárov pre dorast a všeobecných praktických lekárov, aby s ohľadom na požiadavky svojej profesijnej etiky a zodpovednosti venovali potrebnú pozornosť a úsilie **lepšej komunikácii** a poučeniu pri výkone očkovacích úkonov.

Komisia je presvedčená, že národný program povinného očkovania je dôležitý pre efektívnejšie zabránenie diskriminácii osôb zo zdravotných dôvodov. Povinné očkovanie prispieva k **posilneniu hodnôt rovnosti v dôstojnosti i v právach**, ktoré spomína i čl. 12 Ústavy Slovenskej republiky.

Povinné očkovanie je jedným zo spôsobov posilnenia spravodlivého prístupu k zdravotnej starostlivosti, ktorý je zakotvený aj medzinárodnými dohovormi.

Komisia sa domnieva, že obmedzovanie národného programu povinného očkovania predstavuje **významné nebezpečenstvo pre zdravie a životy občanov** Slovenskej republiky, najmä detí, mladistvých a osôb, ktoré z medicínskych alebo iných závažných dôvodov dosiaľ nemohli byť zaočkované.

Komisia je z uvedených dôvodov presvedčená, že všetky zodpovedné štátne orgány by mali vykonať **nevyhnutné kroky na zachovanie národného programu povinného očkovania** a zabrániť jeho podstatnému oslabovaniu.

Text prevzatý z webovej stránky Ministerstva zdravotníctva Slovenskej republiky:
http://www.health.gov.sk/Clanok?eticke-aspekty-povinneho-ockovania-uznesenie-43-51-EK

STANOVISKO K NIEKTORÝM ETICKÝM ASPEKTOM POVINNÉHO OČKOVANIA

Subkomisia pre bioetiku Teologickej komisie Konferencie biskupov Slovenska

Subkomisia pre bioetiku Teologickej komisie Konferencie biskupov Slovenska sa na svojom zasadnutí dňa 26. 10. 2013 opätovne zaoberala etickými otázkami spojenými so zachovaním systému povinného očkovania na Slovensku. Dôvodom boli početné otázky veriacich rodičov a iných osôb nesúcich zodpovednosť za starostlivosť o deti a za ich výchovu, ktorým niektoré osoby alebo mimovládne organizácie pôsobiace v slovenskom verejnom a internetovom priestore predkladajú rozličné pomýlené či deformované „informácie“ týkajúce sa povinného očkovania detí a povinného preočkovania mládeže a dospelých. Pritom sa nezriedka odvolávajú aj na výroky Učiteľského úradu Katolíckej cirkvi, pápežov či Pápežskej akadémie za život, pričom však tieto vyjadrenia svojvoľne prekrucu-

jú alebo nesprávne vysvetľujú. Subkomisia pre bioetiku sa preto cítila povinná zaujať toto stručné stanovisko aspoň k tým etickým aspektom povinného očkovania, ktoré majú v súčasnosti najzávažnejší praktický dosah na oblasť zdravotnej starostlivosti, a tým na život a zdravie detí, mládeže i celej spoločnosti.

1. Subkomisia chce zdôrazniť, že vhodnosť konkrétnych druhov povinného očkovania, očkovacích látok, povinného očkovacieho kalendára, posúdenia medicínskeho a verejno-zdravotníckeho prínosu daného očkovania vo vzťahu k jeho možným rizikám a nežiaducim účinkom vo všeobecnosti, ako aj vo vzťahu ku konkrétnemu dieťaťu, je výsostne odbornou, medicínskou a epidemiologickou záležitosťou. V tejto súvislosti Subkomisia chce povzbudiť i náležite oceniť zodpovednú prácu a kvalifikovaný prístup lekárov, osobitne pediatrov, lekárov pre dorast a ďalších odborníkov, ktorí zabezpečujú potrebné odborné a rozhodovacie činnosti pri zabezpečení prípravy a kontinuálnej realizácie povinného očkovacieho programu, a to v potrebnej spolupráci a pod dohľadom príslušných vedeckých, odborných a regulačných štátnych inštitúcií. Výsledky tohto programu, dosiahnuté na Slovensku v priebehu uplynulých desaťročí, osobitne v období po druhej svetovej vojne až po naše časy, sú právom považované za jeden z najväčších úspechov našej medicíny a organizácie zdravotnej starostlivosti, a to aj v medzinárodnom meradle a porovnaní.

2. Nikto nemá právo zodpovedne prijatý a vedecky podložený odborný úsudok našich lekárov a iných zdravotníkov, odborníkov vo veci povinného očkovania, bezdôvodne či ľahkovážne spochybňovať alebo popierať. Ohrozoval by tým neprípustným spôsobom zdravie, ba i život nevinných, osobitne detí a zdravotne postihnutých alebo oslabených osôb. Subkomisia zároveň vyzýva a žiada lekárov a ďalších odborníkov zúčastnených na príprave a realizácii povinného očkovacieho programu na Slovensku, aby naďalej k tejto svojej práci pristupovali s najvyššou mierou zodpovednosti, odbornej kvalifikovanosti, ako aj s potrebným rešpektovaním etických noriem a mravného rozlišovania.

3. Vo vzťahu k riadne schválenému povinnému očkovaciemu programu majú rodičia voči svojim deťom závažnú morálnu povinnosť im účasť na tomto programe zabezpečiť, a to s ohľadom na ochranu ich zdravia a života. Zároveň tým prispievajú aj k spoločnému dobru celej spoločnosti, na ktorom však majú sami rodičia, ako aj ich deti priamy podiel. Okrem toho poskytujú ochranu aj tým deťom a iným osobám, ktoré nemohli byť z medicínskych alebo časových dôvodov zaočkované. Táto povinnosť je vzhľadom na medicínske a epidemiologické dôvody natoľko závažná, že zo strany zodpovedných štátnych inštitúcií oprávňuje – v záujme dosiahnutia spoločného dobra a s potrebným rešpektovaním dôstojnosti a skutočného dobra každého jednotlivca – vyžadovať plnenie tejto povinnosti aj všeobecne záväznými právnymi predpismi a nariadeniami, vrátane primeraných sankcií, aby sa dosiahlo ich naplnenie. Pochopiteľne, s ohľadom na predpokladanú dobrú vôľu a dobrý úmysel rodičov a iných zodpovedných osôb, ktoré tieto osoby majú mať voči deťom a zvereným osobám, štátne inštitúcie majú uprednostniť, pokiaľ je to možné, skôr prístup vhodnej a zodpovednej osvety, informovanosti a vzdelávania. V tomto smere Subkomisia chce vyzdvihnúť zodpovednosť, povinnosť a nezastupiteľnú úlohu škôl, médií masovej komunikácie a tiež osôb, ktoré sú schopné pozitívne ovplyvniť názory a postoje v spoločnosti.

4. Napokon, Subkomisia sa chce vyjadriť k rôznym nepravdivým tvrdeniam, akoby sa v očkovacích látkach nachádzali súčasti potratených ľudských zárodkov alebo plodov, prípadne akoby sa očkovacie látky z nich alebo s ich použitím vyrábali. V skutočnosti sa pri príprave niektorých očkovacích látok (napríklad na rozmnoženie vírusov, ktoré sa po zneškodnení stávajú súčasťou danej očkovacej látky) používajú bunkové alebo tkanivové kultúry, pri ktorých príprave sa na začiatku, pred mnohými rokmi, použili tkanivá z umelo potrateného ľudského plodu. To je, pochopiteľne, samo osebe, smutnou skutočnosťou, s ktorou z morálneho hľadiska nikdy nemožno súhlasiť, ani ju schvaľovať. Na druhej strane, pokiaľ nie je k dispozícii očkovacia látka, ktorá by bola pripravená s použitím bunkovej alebo tkanivovej kultúry pripravenej eticky vhodným spôsobom, rodičia sú morálne oprávnení, ba povinní – vzhľadom na závažné dôvody ochrany života a zdravia svojho dieťaťa – dať svoje dieťa zaočkovať aj existujúcou očkovacou látkou. Zároveň rodičia majú povinnosť pôsobiť v rámci svojich možností na to, aby sa pri príprave, výrobe, ako aj pri objednávaní očkovacích látok uprednostnili tie, ktoré boli vyrobené eticky vhodným spôsobom. K tomuto úsiliu chce Subkomisia naliehavo vyzvať a povzbudiť aj zodpovedné slovenské štátne orgány a inštitúcie. Rovnako sa Subkomisia s naliehavou žiadosťou obracia aj na samotných výrobcov a distribútorov očkovacích látok, ktorí vzhľadom na svoje možnosti a postavenie majú v tomto smere primárnu morálnu zodpovednosť.

Štrbské Pleso 26. októbra 2013

Mons. Štefan Sečka
predseda Subkomisie pre bioetiku TK KBS

Text prevzatý z webovej stránky Konferencie biskupov Slovenska: http://www.kbs.sk/pdf/KBS/KBS2013Ockovanie.pdf

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STANOVISKO K PREDAJU A VÝDAJU PRÍPRAVKOV HORMONÁLNEJ ANTIKONCEPCIE A INÝCH PRÍPRAVKOV ZAMERANÝCH PROTI ĽUDSKÉMU ŽIVOTU V LEKÁRŇACH

Subkomisia pre bioetiku Teologickej komisie Konferencie biskupov Slovenska

Subkomisia pre bioetiku Teologickej komisie Konferencie biskupov Slovenska, reagujúc na početné otázky kresťanských farmaceutov, ktorí vykonávajú svoje povolanie na území Slovenska, sa na svojom zasadnutí dňa 26. októbra 2013 opätovne zaoberala mravnými problémami, ktoré predstavuje predaj alebo výdaj farmaceutických prípravkov určených na hormonálnu antikoncepciu, vrátane takzvanej núdzovej (postkoitálnej) antikoncepcie. Komisia konštatovala, že ide o závažný problém profesijnej etiky tak pre kresťana - farmaceuta, ktorý je majiteľom lekárne, ako aj pre farmaceuta, ktorý je ako zamestnanec lekárne nútený, aby takéto prostriedky predával alebo vydával.

Odvolávajúc sa na morálnu náuku Katolíckej cirkvi, potvrdenú aj novšími vyjadreniami pápežov Jána Pavla II. (1) a Benedikta XVI. (2), Subkomisia vydáva toto stanovisko:

1. Lekárnik pri poskytovaní farmaceutickej starostlivosti predstavuje dôležitý odborný článok vo vzťahoch medzi lekárom, liekom a pacientom. Nie je iba predajcom alebo vydávajúcim liekov a zdravotníckych pomôcok, ale vykonáva aj veľmi dôležitú odbornú konzultačnú činnosť vzhľadom na správne a bezpečné použitie lieku, jeho účinky, nežiaduce účinky a prípadné interakcie. Zanedbaním tejto povinnosti by mohol užívateľovi lieku spôsobiť poškodenie zdravia, prípadne ohroziť jeho život. Informovanie používateľa lieku – pacienta zo strany farmaceuta mu-

sí byť predovšetkým pravdivé, úplné a dostatočne zrozumiteľné. Farmaceut pri výkone svojho povolania nikdy nesmie konať proti ľudskému životu alebo zdraviu – a vždy musí rešpektovať ľudskú dôstojnosť, práva a morálne oprávnené záujmy pacienta. Pre farmaceuta – kresťana je navyše plnenie týchto povinností vecou kresťansky informovaného a formovaného svedomia a prejavom kresťanského svedectva.

2. Katolícka cirkev stojí jednoznačne na strane rešpektovania a ochrany každého ľudského života od jeho počatia až po prirodzenú smrť. Preto podporuje taký vedecký výskum a technologický pokrok, ktorý je v záujme života a zdravia človeka a ľudského spoločenstva a ktorý zároveň dôsledne rešpektuje etické požiadavky vyplývajúce z nenarušiteľnej dôstojnosti človeka, jeho života, zdravia, ľudských práv a mravne oprávnených záujmov. Rýchly rozvoj biomedicínskych vied a technológií však prináša, okrem prospechu pre zdravie a život človeka, žiaľ, aj nové formy agresie proti ľudskému životu a proti dôstojnosti ľudskej osoby. Medzi takéto skutočnosti patria aj farmaceutické prípravky, ktoré sú určené na hormonálnu antikoncepciu, vrátane takzvanej núdzovej (postkoitálnej) antikoncepcie. Morálne zlo použitia antikoncepčných prostriedkov je okrem samotného antikoncepčného úmyslu a účinku (3) spojené aj s ich postfertilizačnými (menej presne abortívnymi) účinkami (4), ktoré sa uplatňujú po oplodnení (fertilizácii) a spôsobujú smrť počatého ľudského jedinca – ľudského zárodku (embrya). Ide teda o priamy útok voči konkrétnemu ľudskému životu v prvých dňoch jeho existencie, či už si to žena používajúca „antikoncepčné" prostriedky uvedomuje, alebo nie. Predajom alebo výdajom takýchto farmaceutických prostriedkov farmaceut priamo spolupracuje na závažnom morálnom zle a nesie za to aj vlastnú morálnu zodpovednosť. Túto nemôže jednoducho presunúť na používateľa alebo na kupujúceho, či na predpisujúceho lekára. Preto má farmaceut – kresťan vo svedomí povinnosť odmietnuť výdaj alebo predaj týchto prípravkov. Majiteľ lekárne, ktorý nesie primárnu zodpovednosť za sprostredkovanie tovaru vo svojej lekárni, má vo svedomí povinnosť odmietnuť objednávanie a predaj takýchto prostriedkov (5).

3. Povinnosť kresťana – farmaceuta odmietnuť účasť na výdaji, distribúcii, objednávaní alebo predaji je ešte zrejmejšia v prípade prípravkov určených na vykonanie umelého potratu (6), ako aj iných prípravkov zameraných proti ľudskému životu, pokiaľ by sa tieto azda na trhu v Slovenskej republike objavili (7).

4. Vzhľadom na niektoré účinky liečiv (hormónov) obsiahnutých v prípravkoch hormonálnej antikoncepcie môže byť, v osobitne indikovaných prípadoch, prípustné ich použiť ako terapeutický prostriedok. V takomto osobitnom prípade môže farmaceut po poskytnutí úplnej a zrozumiteľnej informácie o lieku, s výslovným upozornením na jeho postfertilizačné (abortívne) účinky, sprostredkovať jeho výdaj, pokiaľ je na lekárskom predpise uvedená zodpovedajúca diagnóza. Kresťanskí manželia musia pri takomto užívaní daného prípravku vždy vziať do úvahy spomínané postfertilizačné (abortívne) účinky a zachovať v potrebnej miere sexuálnu abstinenciu.

5. Kresťanom, kresťanským inštitúciám, organizáciám a zariadeniam, ako aj všetkým ľuďom dobrej vôle vzniká v súvislosti s vyššie uvedenými požiadavkami závažná morálna povinnosť uprednostňovať a podporovať všetkými vhodnými prostriedkami farmaceutov a lekárne, ktoré uplatňujú a rešpektujú výhrady svedomia a zásady profesijnej etiky farmaceuta vo vzťahu k ochrane ľudského života a zdravia.

Štrbské Pleso 26. októbra 2013

Mons. Štefan Sečka
predseda Subkomisie pre bioetiku TK KBS

1. Ján Pavol II., príhovor k členom Medzinárodnej federácie katolíckych farmaceutov (3. novembra 1990). **2.** Benedikt XVI., príhovor k účastníkom 25. medzinárodného kongresu katolíckych farmaceutov (29. októbra 2007). **3.** Porovnaj Katechizmus Katolíckej cirkvi, čl. 2370, 2399. **4.** Hoci deklarovaným hlavným mechanizmom účinku prípravkov hormonálnej antikoncepcie, či už podávanej perorálne, injekčne, transdermálne, alebo zavedením vaginálnych krúžkov alebo implantátov, je blokovanie ovulácie (uvoľnenie zrelého vajíčka z vaječníka ženy), uplatňuje sa aj účinok podaného hormónu/hormónov na vlastnosti výstelky a pohyb vajcovodov, ako aj na vlastnosti výstelky maternice (endometria), čím sa dosiahne zabránenie uhniezdenia živého ľudského zárodku (embrya) v maternici a jeho usmrtenie (postfertilizačný účinok). Hormonálna antikoncepcia bez postfertilizačného (menej presne abortívneho) účinku v súčasnosti neexistuje. **5.** Ide o uplatnenie výhrady svedomia – bližšie pozri Ján Pavol II., encyklika Evangelium vitae (25. marca 1995), č. 73 – 74. Pozri aj Ústava Slovenskej republiky, čl. 24 ods. 1; Základná zmluva medzi Svätou stolicou a Slovenskou republikou, čl. 7; Zákon 578/2004 Z. z. o poskytovateľoch zdravotnej starostlivosti, zdravotníckych pracovníkoch, stavovských organizáciách v zdravotníctve a o zmene a doplnení niektorých zákonov, Príloha č. 4 Etický kódex zdravotníckeho pracovníka. **6.** Porovnaj Vyhlásenie Subkomisie pre bioetiku TK KBS zo dňa 16.2.2013 a vyhlásenie predsedu KBS zo dňa 11.1.2013. **7.** Napríklad prípravky, prostriedky alebo pomôcky na vykonanie eutanázie alebo asistovanej samovraždy.

Text prevzatý z webovej stránky Konferencie biskupov Slovenska:
http://www.kbs.sk/pdf/KBS/KBS2013HormAnt.pdf

MEDICAL RESEARCH FOR AND WITH OLDER PEOPLE IN EUROPE

(Part II)[1]

European Forum for Good Clinical Practice,
Geriatric Medicines Working Party

3.5 THE COMPOSITION OF THE ETHICS COMMITTEE IN GERIATRIC TRIALS

All members of the research ethics committee including geriatric experts consulted on an ad hoc basis should be independent of the sponsor, the investigator and the research proposed. The qualifications and expertise of the experts used and the members of the research ethics committee should be documented and annexed to its opinion. Geriatric expertise should be available when reviewing the initial protocol and the subsequent amendments, as well as the follow-up of the study, until submission of the final report.

Research ethics committees specialised in geriatrics could be considered for the evaluation of trial protocols that are complex or in serious geriatric diseases. Such committees normally also include laypersons, some of whom may be representatives from the civil society.

3.5.1 Examples of geriatric expertise

Geriatric expertise goes beyond having professionally worked with older patients and could be defined on the basis of education, training and experience in the various aspects of ageing, ethics and psychosocial aspects. Therefore, this would include i) physicians with geriatric qualifications; ii) geriatric ethicists; iii) geriatric pharmacologists; iv) qualified geriatric nurses or psychologists, etc. In addition to their qualifications, it is recommended that the experts demonstrate at least some years of experience in geriatric care and direct experience of clinical trials with older patients in similar age groups, for example as an investigator in several trials performed in the older patient of similar age groups. If this cannot be found in

[1]Editorial note: Continued from No. 1-2/2013.
The full text available at the EFGCP webpage: www.efgcp.be

one individual, two or more geriatric or gerontologist experts could contribute to the expertise needed. Expertise used should be documented and recorded by the research ethics committee.

3.5.2 Opinion on the protocol

The opinion will be based on, the following points:

- The need to investigate the particular indication/therapeutic to prevent the generation of area/disease, in order useless or redundant data.
- Whether the trial replicates similar trials based on an identical hypothesis (which should be avoided).
- That the protection and safety of any older patient is ensured, including minimisation of risks, fear pain and distress, and that appropriate geriatric expertise is available at all trial sites.
- Justification is provided for the inclusion of the older patient to achieve the trial objectives.
- That appropriate non-clinical data are available before the use of the product in older patients. This may include data from old animal studies, modelling or other predictive studies.
- Whether there is an extensive and comprehensive review of available evidence (including relevant publications). Any experimental work on the investigational medicinal product should be available and reviewed to justify the initial hypothesis, the safety and the evaluation of expected benefit. The difference expected versus comparators should be described.
- The quality of the performance of the trial is such that it is likely that the results will be interpretable; monitoring, audit and quality assurance are described.
- When justified, an independent Data and Safety Monitoring Board (DSMB) with appropriate expertise should be planned consistent with regulatory guidelines.
- There are provisions in the protocol for systematic independent publications of results, within a reasonable timeframe, including when results are unfavourable.
- The protocol includes provision of the medicinal products to patients involved in trials after the completion of the trial where appropriate, unless the benefit to risk balance of the medicinal product tested proves negative.
- The research ethics committee and the competent authority should ensure that the sponsor regularly monitors and re-examines the balance of benefit/risk of the research so that the health and well being of the older and vulnerable people enrolled are safeguarded.
- For randomised trials there should be equipoise ("genuine uncertainty within the expert medical community [...] about the preferred treatment") at the beginning of the trial and no participants should receive care known to be inferior to existing treatments. To help research ethics committees in reviewing geriatric trials, Annex 2 provides a list of the aspects to be taken into consideration when reviewing a clinical trial to be performed in the older and vulnerable population.

4. THE DESIGN OF CLINICAL TRIALS CONDUCTED WITH THE GERIATRIC POPULATION

4.1 DESIGN AND ANALYSIS

The clinical trial design depends on the objective(s) of the trial and the scientific question(s) to be answered. If the trial is conducted with a view to providing data for regulatory purposes, reference should be made to scientific guidelines for drug development in older patients, including EMA guidelines. In general it is preferable to include both non-geriatric and geriatric patients in the same study(ies), which can facilitate observation of age-related differences. In some cases a separate study in the geriatric population can be preferable.

An appropriate representation of the geriatric population, including patients with co-morbidities and concomitant therapies should be enrolled in a clinical development programme to characterise the safety and efficacy of the drugs and allow application to everyday practice.

Clinical trials involving older people should reflect the importance of specific end-points such as quality of life, functional capacities, compression of morbidity and clinically relevant measures.

An appropriate comprehensive geriatric assessment could be used as criteria for randomization and for outcomes in designing clinical trials.

Research in the setting of palliative care will look at the complex quality of life issue in relation with the end-points for interventions where the older population QoL becomes more important than chronological length of survival, particularly in the frail very old.

To ensure the feasibility of clinical trials to be performed, it is recommended that the trial design be set up following consultation of the older patients to be involved in the trial, or with patient representatives. As is the case for trials in younger adults, all measures to avoid bias should be included in trials performed in the older population. For example, unblinded and/or uncontrolled trials for the demonstration of efficacy are subject to increased bias and should be avoided whenever possible.

Whenever possible (e.g. when differences in product mode of administration are impossible to mask), open trials should include provisions for blinding of assessment. Assessment, i.e., a systematic evaluation and documentation, in many cases will be based on the assessment by relatives or other carers, but in most circumstances the evaluation by the older patients themselves will be appropriate.

Trials without a control group for demonstration of efficacy should be avoided in principle. They have limited usefulness for the demonstration of safety, unless they are used prospectively for longitudinal studies or in predefined subgroups.

Alternative (less conventional) designs and/or analyses should be justified and it is recommended that they should be agreed with competent authorities when used with a view to provide data for regulatory purposes.

Modelling and simulation (M&S) methods can be used in place of clinical trials (CTs) in some cases (e.g. to generate appropriate data and avoid unnecessary use of older patients in CTs) and the use of such methods should be formalized in guidance.

The size of the trial conducted in the older patients should be large enough to demonstrate the appropriate efficacy with sufficient statistical power, recognizing the consideration of a higher dropout rate. In consideration of the analysis of risks and benefit, trials involving fewer older patients should be weighed against trials involving more patients but using less invasive procedures. Adaptive, Bayesian or other designs may be used to minimise the size of the clinical trial.

4.2 GERIATRIC CONTROL GROUPS

The use of control groups, including the use of placebo and/or active comparator, should be based on equipoise[1]

(32), should be appropriate to the condition(s) under investigation in the trial. It should be justified on scientific and ethical grounds, consistent with ICH GCP and the Declaration of Helsinki.

4.2.1 Use of comparator

Use of placebo in the older adults is more restricted than in younger adults, because some older patients cannot consent, and may not understand their use and purpose.

The use of placebos should only be allowed when it does not mean withholding effective treatment, particularly for serious and life threatening conditions. The use of a placebo is often needed for scientific reasons, including in geriatric trials. The use of a placebo may be warranted when evidence for any particular treatment is lacking or when the placebo effect is known to be very variable (e.g. pain). As the level of evidence in favour of an effective treatment increases, the ethical justification for placebo use decreases.

The use of a placebo is not equivalent to the absence of treatment, for example it could be used as well as standard care. In all cases, its use should be associated with measures to minimise exposure and avoid irreversible harm, especially in serious or rapidly evolving diseases. As appropriate, rescue[2] treatment and escape procedures[3] should be set up.

Other situations where the use of placebo should be scrutinised and challenged, include run-in periods where a protocol requires active treatment to be withheld. Situations in which a placebo may be considered as a comparator, for example, might be when there is no commonly accepted therapy for the condition and the investigational medicinal product is the first one that may modify the course of the disease process, or when the commonly used therapy for the condition is of questionable efficacy or carries with it a high frequency of undesirable adverse reactions and the risks may be significantly greater than the benefits.

Other trial designs should be considered if appropriate. Active-control trials may be more difficult to interpret than placebo-controlled ones but may provide useful information on comparative benefit/risk balance. Therefore it is as important to discuss the exclusion of placebo, as it is to discuss its inclusion for geriatric clinical trials.

4.2.2 Superiority versus non-inferiority trials

Equivalence and non-inferiority trials, and in particular the choice of equivalence or non-inferiority margins in relation to sample sizes feasible in the geriatric population, raise issues such as variability (add references), and should be fully justified when used instead of superiority trials. In addition, inconsistent trial conduct may further blur differences between treatments in equivalence or non–inferiority trials. Existing guidelines on methodology issues and/or specific EMA guidelines per therapeutic area should be consulted.

4.2.3 Comparative effectiveness research

The issue of comparative effectiveness study is also relevant to research in geriatric medicine and is being pursued at the European level (33).

[1] Also known as the principle of equipoise, provides the ethical basis for medical research that involves assigning patients to different treatment arms of a clinical trial. The term was first used by Benjamin Freedman in 1987.[1]

[2] Rescue refers to treatment that may be given on top of trial medications to avoid danger or distress, for example pain treatment, as soon as the patient reaches a defined level.

[3] Escape refers to prompt removal of subjects whose clinical status worsens or fails to improve to a defined level in a trial.

4.3 PAIN, DISTRESS AND MINIMISATION OF FEAR

Physical, emotional and psychological distress should be prevented as much as possible, and effectively treated when unavoidable. This requires that physical pain and distress intensity is assessed and regularly monitored according to guidelines and appropriate validated scales, particularly in older patients who cannot express it. Effective treatment in relation to the intensity of pain should be administered and reviewed regularly on the basis of the assessments performed. In addition, if sedation is needed, monitoring should be set up and the appropriate level of sedation needed for the procedure(s) should be maintained.

Painful and invasive procedures should be minimised. Population approaches and sparse sampling for pharmacokinetic data may reduce the number of blood samples in older subjects.

Appropriate explanations should be given to the older research participant/patient prior to any investigation or procedure, in order to decrease anxiety and anticipation of pain, in honest, but not frightening terms. Any procedures that might also lead to embarrassment of the older patients (such as undressing) should be avoided or explained. In order to minimise pain, distress, and fear, facilities should be appropriate for older patients care, and the personnel should be trained to look after older patients and supervised by experienced health care professionals. Staff should be trained to communicate with legal representatives and with older patients. Older patients in a trial should be hosted in a familiar environment, including appropriate furniture, activities, where appropriate, and skilled personnel should address their concerns.

The variability of response to pain, distress and fear between older patients should be taken into consideration. Different reactions may be expected, when older people are affected by a chronic or acute disease.

4.4 RISK ASSESSMENT AND MONITORING

The interest of all patients should always prevail over that of science and society. This is paramount when assessing and monitoring risks. Risks are to be viewed in balance to the benefit (**Annex 12**).

Older people who are not able to consent should not be included in a research study that has no likelihood of benefit for them, unless this research cannot be performed instead with patients capable to consent, and the research results only in minimal risk and burden to promote the condition of the patient population represented by these older research participants. There may be circumstances where research may be performed on such patients provided that that both the legal and or appropriate representative has given consent.

4.4.1 Assessment of risk

Risk assessment is a crucial step in evaluating a protocol and conducting the trial. Risk is defined as potential harm (real or theoretical) or potential consequence of an action. It may be physical, psychological, or social, and may be immediate or delayed. It may vary according to age groups. Risk should be assessed in terms of probability, magnitude and duration. Geriatric trials should be analysed for potential risks, including those that may not usually be of concern in younger adults because medicines or procedures may cause adverse effects in older participants that have not been identified in young adults.

It is the responsibility of the investigator to make a thorough analysis of the risks in the trial and to describe this in the protocol so that research ethics committee may de-

termine whether to provide a favourable opinion or not. Risks are not limited to physical harm; they may include psychological and relating to information (e.g. genetic diagnosis) risks.

The unavailability of appropriate geriatric formulations may also incur risks. Disclosure of a risk for an incurable disease or violation of privacy may also cause potential harm.

Risk assessment includes the evaluation of the risk of the medicinal product tested or the control substance, the risk of withholding active treatment in some cases and the risk of the disease itself. Potential harm may include invasive procedures and the intrusiveness of research processes and demands, the severity and seriousness of potential harm, the reversibility of adverse effects and reactions, and their preventability. The accumulation of research projects in the same population (over-studied population) is another source of potential harm. Multiple clinical trials in an individual should be discouraged.

In the case of emerging issues during a trial with potential conflict between the older patient's interest and research interest, the protocol should envisage the management of such issues, e.g., harm in giving versus harm in withholding treatment. In addition to the risk inherent to the trial, there is a need for evaluation of external risks, for example linked to the centres involved with variable level of expertise and/or experience.

Risk assessment is difficult in practice as probabilities are unknown; the elements that influence the risks should be identified in the protocol. Finally, any identified risk should be associated to measures to prevent, minimise and monitor such risks as much as possible.

The participant must always be made aware of these arising conflicts and given the opportunity to withdraw.

The determination of the levels of risk and the associated potential benefits are the basis for ethical approvability. The following distinct risk levels are proposed as a means to decide on the ethical acceptability of trials:

- Minimal risk, which could be defined as probability of harm or discomfort not greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
- Minor increase over minimal risk.
- Greater than minor increase over minimal risk.

4.4.2 Monitoring the level of risk

The level of risk may evolve over time, during the trial and with developing knowledge. It is important to evaluate also whether the risks differ by age e.g. impairment of renal function. Risk should be continuously monitored and pre-specified in the protocol. Rules about the stopping of the trial should be included in the protocol, especially for unscheduled or scheduled analyses in relation to safety or non-compliance.

Certain studies require the use of a Data and Safety Monitoring Board (DSMB), which should be consistent with regulatory guidance document. The DSMB should benefit from geriatric expertise.

In line with the Clinical Trials Directive, the sponsor of the clinical trial should identify and assess the risks (real and theoretical) and harm induced by the investigational medicinal products in the safety report submitted once a year throughout the clinical trial, or on request, to the competent authority and the relevant research ethics committee of the concerned Member States. In this report the sponsor should perform a specific analysis of the subjects' safety in the geriatric population enrolled in the clinical trial, and provide an update of the benefit-risk evaluation for the geriatric population, in the light of scientific developments or events arising in the course of the research.

4.5 BENEFIT AND MEASURES OF BENEFIT

Direct benefit refers to benefit for the individual and/or benefit for the group. For the purpose of this document, the term "indirect benefit" is not used.

Benefit can be defined as progress in treatment, diagnosis, or prevention for the older subjects or the group of older patients affected. It is a tangible outcome that may be experienced by the subject. This may be obtained through either increased efficacy or safety resulting in a better benefit-risk balance, or through the provision of an alternative to existing treatment with at least similar expected benefit risk balance. Benefit can also be obtained through a contribution to patient care (for example, better route of administration, decreased frequency of dosing, improvement in relation to potential mediation errors or compliance, reduced treatment duration, or a clinically relevant formulation).

Benefit for the group, i.e., older patients affected by the same disease, or a disease which shares similar features and for which the medicinal product may be of benefit, could be defined by increased knowledge of the condition and /or treatment, which would possibly result in better diagnosis, treatment or prevention. Measures of such benefit would include the importance of knowledge gained, severity of the issue to be addressed, whether the issue is common or not, the likelihood of obtaining results from the proposed research, and the usefulness of benefits obtained.

4.5.1 Balance of benefit and risk

The determination of the levels of risk and the associated benefits are the basis for ethical approval. The risk levels should be presented by the sponsor and assessed by the research ethics committee. As the assessment of the risk and the benefit may be based on probabilities and assumptions, respectively, this should also be balanced with the severity of the condition or diseases to be studied and the benefit and risk of alternative treatments. In the following examples, levels of risk are considered to be in balance with the benefits for a trial with the geriatric population:

- Minimal risk with benefit for the individual or benefit for the group.
- Minor increase over minimal risk, with benefit to individual or benefit to the group, and with the benefit to risk balance being at least as favourable as that of available alternative approaches.
- Greater than minor increase over minimal risk with benefit for the individual that is especially favourable in relation to available alternative approaches for the individual's condition.

4.6 ASSAYS IN RELATION TO THE PHYSIOLOGICAL STATE OF THE OLDER PATIENT

Assays, investigations and blood sampling volumes related to the trial should be described and justified in the protocol.

The number and type of assays and investigations should take into consideration the physiological condition of any older patient to be included in the trial, especially their renal and hepatic function: appropriate facilities and material should be used. Alternative sampling (e.g. urine or saliva sampling) for pharmacokinetic studies should be preferred when possible. In principle, general and/or local anaesthesia should be used as appropriate

for painful and/or invasive procedures. Timing of sampling should be co-ordinated as far as possible to avoid repeat procedures and to avoid repeat sampling during the day in order to minimise pain and distress, and the risk of iatrogenic complications. Trained staff should perform sampling. The number of attempts for sampling should be limited. Timing of sampling and number of sampling attempts should be defined in the protocol. For example, it is recommended that after one unsuccessful attempt, another experienced person take over the procedure.

5. TRIALS WITH HEALTHY OLDER PARTICIPANTS

Many relatively healthy 70 year-olds and over take different medications and may therefore be excluded from healthy volunteer studies although they are representative of this population.

Some studies need to be performed in very old people when variability is very high, who are healthy at the time of the trial. Prevention trials or geriatric vaccine trials, including immunogenicity studies, will fall into this category but include the target population likely to benefit. Trials in older persons with intermittent diseases (e.g., flare-ups or seizures) are acceptable because even in the "healthy" phase older subjects are affected. Whenever possible the younger old people and less frail should be considered for inclusion before the older old or the frail.

6. INDIVIDUAL DATA PROTECTION

As in other patient populations, high standards of privacy, security and data protection, as well as respect for research participants' rights, must be observed.

The confidentiality of medical records must be protected in accord with applicable laws including data protection laws.

Where personal information on older patients is collected, stored, accessed, used, or disposed of, the researcher should ensure that the privacy, confidentiality and cultural sensitivities of the subject and the community are respected. Older patients participating in a trial are entitled to know any information collected on their health. Other personal information collected for a research project can be made accessible to them if they so wish in conformity with national laws on the protection of individual data.

7. UNNECESSARY REPLICATION OF TRIALS

It is considered unethical to replicate unnecessarily trials in the older and very old patients. This can only be avoided by ensuring that information gained in any trial is made available to researchers and the public.

7.1 PUBLICATION OF GERIATRIC TRIALS AND RESULTS

Registration of geriatric clinical trials and publication of results including unfavourable ones, together with a thorough analysis of the literature should allow detection of similar trials, with similar aims, and thus prevent unnecessary duplication of trials in the older patients.

7.2 INTERNATIONAL DATABASE AND AVAILABILITY TO THE PUBLIC

There is an ethical duty to check whether existing knowledge is available to modify the initial hypothesis for the trial. Public access to ongoing and completed trials through existing databases will facilitate avoiding replicating unnecessarily trials in older patients.

8. ADVERSE REACTIONS AND REPORTING

Rules and obligations for adverse reactions reporting in geriatric trials are identical to those in younger adults, in particular, but not exclusively, the notification of serious adverse reactions observed in clinical trials. The EU pharmacovigilance Regulation and its provisions should contribute to improving adverse events reporting through RMPs (Risk Management Plans) and PASS (Post Authorization Safety Studies).

As adult data are poorly predictive of safety in the older patients, reporting may cover target organs and types or severity of reactions differing from that expected in adults. A specific assessment of the adverse reactions associated with the administration of the investigational medicinal product in the older subjects should be performed in the annual safety report.

9. INSURANCE ISSUES

Insurance is mandatory according to the Clinical Trials Directive (Article 3(f)). Obtaining insurance for trials performed in older patients may be challenging, for example, because of different insurance regulations in Member States. Research ethics committees should pay careful attention to the insurance document.

10. TRIALS IN OLDER PATIENTS IN NON-EU COUNTRIES

According to Directive 2001/83/EC as amended by Directive 2004/27/EC, clinical trials submitted in a marketing authorisation application in the EU, which were performed in non-EU countries, should be conducted in accordance with the principles of Good Clinical Practice and the ethical requirements equivalent to the provisions of Clinical Trials Directive and should comply with good manufacturing practices of EU countries. These principles should also apply for geriatric trials where the medicinal product is not studied with a view to obtaining a marketing authorisation. The laws and regulations of the countries in which the trials are carried out should be respected.

Ethical standards should be no less exacting than they would be for research carried out in countries EU, and the trial documentation should be submitted for ethical and scientific review in the EU Member State in which the sponsor resides and in the host country.

The trial should ensure that it responds to the public health needs and priorities of the country in which it is carried out. It is the responsibility of all involved parties to ensure that this is respected and that the geriatric specificities, including assent are obtained for the older patients.

The recommendations in this document should be followed by EU researchers and sponsors, carrying out trials in third countries, as well as by ethics committees reviewing such trials or their results.

11. ETHICAL VIOLATIONS AND NON-COMPLIANCE WITH GOOD CLINICAL PRACTICE

GCP compliance of clinical trials is required. Although not specific to geriatric trials, ethical violations and non-compliance with GCP is particularly important, as some older people are a vulnerable population. There is a role for research ethics committees and competent authorities in case of violation and non-compliance with GCP. Violations fall into critical, major and minor issues, according to whether and to which extent patient safety and scientific value are compromised. The preferred option to avoid such violations is education, training and counselling. Research ethics committees should liaise with

competent authorities if they are informed of such violation or non-compliance.

Compliance with GCP should be explicit in publications, and results of studies conducted unethically should be made public with a clear warning specifying the unethical aspects. Information on such trials is needed to avoid unnecessary repetition of the trials and to protect future trial participants. If non GCP-compliant data are submitted as part of a marketing authorisation application, the quality of the data, the study results, and consequently the validity of the marketing authorisation application should be scrutinised. Sensitivity analysis should be performed within the GCP-compliant full data set, and in some cases also in comparison with all GCP-non-compliant data. The overall reliability of the trial should be questioned. Subsequent measures (including initial review) should be taken in accordance with national legislation, if appropriate.

12. ANNEX 1: LIST OF ISSUES FOR A TRIAL WITH THE GERIATRIC POPULATION

List of issues to be taken into consideration for planning a geriatric trial:

1. Identification and scientific validity of the study question to be answered.
2. Justification of the study to be performed in the older people.
3. Evidence of direct benefit for the older subjects, or benefit for the group.
4. The competence of the responsible study investigator and his/her team.
5. The infrastructure of the institution or primary care practice that should be qualified and experienced in geriatric research in general and in particular in the field of the applied project.
6. The pre-clinical safety and efficacy data (investigator's brochure, available literature) that are preconditions for a geriatric clinical trial.
7. The clinical results of adult studies (literature, investigator's brochure), if any.
8. Type and phase of the study.
9. Use of placebo or active control.
10. Appropriate formulations of medicinal products.
11. Appropriate scales or measures of end-points (e.g., pain scale).
12. Study design and biometric planning in relation to the trial question.
13. Design feasibility and information sheets checked with older/patient representatives.
14. Inclusion and exclusion criteria.
15. Statistical methods.
16. Criteria for the termination of the study.
17. Safety measures including the set-up of a Data Safety and Monitoring Board (DSMB).
18. Appropriate pharmacovigilance procedures are put in place by the sponsor.
19. Study risks, pain, fear and discomfort.
20. The potential risks (real and theoretical) have been weighed against the expected benefits for the older person enrolled in the clinical trial. The balance of expected benefits versus risks should be positive for the clinical trial.
21. Comprehensive, understandable Informed Consent and Information sheets for legal representatives.
22. Understandable age specific Informed Assent and Information sheet.
23. Anonymity of the data, as well as confidentiality of personal information related to the older subjects involved in the research, and to his/her family.
24. Insurance of older participants, in the relevant country.
25. If available, opinions of other ethics committees for international multicentre studies.
26. Publication of trial results.
27. Continuation of trial medication where appropriate.

13. ANNEX 2: INFORMATION FOR INFORMED CONSENT

Information sheets should be separate for older patients /participants (and their legal representatives if necessary) whenever a protocol is specifically geared to the involvement of such patients: they should be concise in content, precise in language (e.g., use of non-technical terms), and appropriate for the older patients/participants (e.g., avoid abstract concepts, multiple options). The number of variations of information sheets should be kept to a minimum required to include substantially different wording or presentation. In addition, information sheets should not cause unnecessary distress. They should possibly be designed with participants, affected older patients. Information sheets should be harmonised throughout sites in multi-centre trials, and address similar age groups in multinational trials.

List of items recommended to be covered in the information sheets:

1. What is the purpose of the trial?
2. Why have I been chosen?
3. Do I have to take part?
4. What will happen to me if I take part?
5. What are the compensations?
6. What will I have to do?
7. What is the medicine that is being tested?
8. What are the alternatives for diagnosis or treatment?
9. What are the possible disadvantages and risks of taking part?
10. What are the side effects of any treatment received when taking part?
11. Is ionising radiation to be received, and which regulations are respected?
12. What are the possible benefits of taking part?
13. What happens when the research study stops?
14. What if there is a problem?
15. Will my taking part in the trial be kept confidential?
16. What will happen if I don't want to carry on with the trial?
17. What are the options if I stop taking part in the trial?
18. How is my General Practitioner/Family doctor involved?
19. What will happen to any samples taken from my body?
20. Will any genetic tests be done?
21. What will happen to the results of the research trial?
22. Who is organising and funding the research?
23. Who has reviewed the trial and what are the results?
24. Contact details for information or complaints.

14. ANNEX 3: EXAMPLES FOR LEVELS OF RISKS

The following table provides examples of risk evaluation of measures carried out for the purpose of a trial. For example, an existing central venous line may reduce the pain and invasiveness of blood sampling, but also increases the risk of infection and of excess blood losses with line handling.

The risk evaluation of some of the measures (including, but not limited to those marked*) is very much dependent on such circumstances and on the context of its use in the trial. In addition, the risk level increases with the increase in frequency of the measures and with the susceptibility to harm of involved/exposed organs. The categorisation proposed in the table applies to single or very infrequent use of the measure. The examples presuppose that the measures are carried out to the highest professional standards.

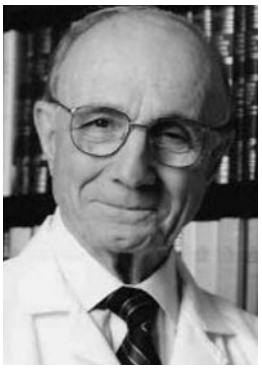
References

See Part I of the document in Med. Etika Bioet., Vol. 20, 2013, No. 1-2, p. 15.

No or minimal risk	history taking, clinical examination, behavioural testing, psychological testing*, quality of Life assessment
Minor increase over minimal risk	venipuncture*, finger prick*, subcutaneous injection, breath condensate collection, collection of saliva or sputum, collection of hair sample, collection of tissue removed from body as part of medical treatment*, topical analgesia*, stool tests, bio-impedancemetry, transcutaneous oxygen saturation monitoring (pulse oxymetry)*, blood pressure monitoring, electroencephalography, electrocardiography, vision or hearing testing, ophthalmoscopy, tympanometry, lung function tests (peak flow, exhaled NO, spirometry), oral glucose tolerance test,ultrasound scan, digitally amplified chest or limb X-ray*, stable isotope examination, arterial puncture, PH metry, nasogastric tube insertion and use, transcutaneous oxygen or carbondioxide tension monitoring, electrophysiological measurements (using stimulation), exercise testing (ergometry, spiroergometry), pulmonary function testing, peripheral venous lines, polysomnography, fasting (≥ 1 meal)
Greater than minor increase over minimal risk	urine collection with bag, urine collection via endoluminal or suprapubic catheter, spinalCSF tap, bone marrow aspiration, MRI scan, X-ray other than digitally, amplified chest or limb X- ray, CT scan* ity, X-ray DEXA bone density measurement, use of contrast media, paracentesis, skin punch biopsy, airways or skin hyperactivity challenge test, heart catheterisation, endoscopy, biopsy, surgery or modification of standard surgical procedure carried out as part of medical treatment, sedation, anaesthesia, systemic analgesia, hypoglycaemia test, unstable isotope usage, PET scanning

Prof. Edmund Pellegrino MD (1920 – 2013)

Considered one of the founders of bioethics and an early pioneer in teaching humanities in medical schools, he was the author of more than 600 published articles in medical science, philosophy and ethics and author or co-author of 23 books.
Born June 22, 1920, he received his bachelor's of science degree from St. John's University and his M.D. from New York University. He served residencies in medicine at Bellevue, Goldwater Memorial, and Homer Folks Tuberculosis Hospitals, after which he was a research fellow in renal medicine and physio-logy at New York University.



When he was appointed the John Carroll Professor of Medicine and Medical Ethics at Georgetown University in 1982, Pellegrino had already served as chair and medical director at the Hunterdon Medical Center in New Jersey. He also had served as founding chair of the Department of Medicine at the University of Kentucky, chancellor and vice president for the health sciences at the University of Tennessee, president of the Yale-New Haven Medical Center, and president of The Catholic University of America.
At Georgetown University he served as founding director for the Center for the Advanced Study of Ethics as well as the Center for Clinical Bioethics, and as interim chair of the university's Division of Internal Medicine at Georgetown University Medical Center. He also was a former director of the Kennedy Institute.
Dr. Pellegrino was the founding editor of the Journal of Medicine and Philosophy, a master of the American College of Physicians, a fellow of the American Association for the Advancement of Science, and a member of the prestigious Institute of Medicine of the National Academy of Sciences. In the course of his lifetime, he was the recipient of 54 honorary doctorates.
In 2004, Pellegrino was named to the International Bioethics Committee of UNESCO, and he served as chair of the President's Council on Bioethics from 2005-2009. In his 90s, he was still mentoring students, attending rounds in MedStar Georgetown University Hospital, writing articles and speaking nationally and internationally.
"Medicine is a moral enterprise," he told Georgetown Magazine in 1996, "and if you take away the ethical and the moral dimensions, you end up with a technique. The reason it's a profession is that it's dedicated to something other than its own self-interests."
The editor of this journal had the privilege of enjoying several lengthy encounters and friendly discussions with Dr. Pellegrino during his stay at the Kennedy Institute as a Fulbright fellow in 2000. In him he found his lifetime personal model both as a physician and as a bioethicist.

Prof. Jozef Glasa MD, PhD, Editor ME&B

Medicínska etika & bioetika - Medical Ethics & Bioethics. Medzinárodný, dvojjazyčný, vedecko-odborný časopis pre otázky medicínskej etiky a bioetiky. Je určený najširšej medicínskej a zdravotníckej verejnosti v Slovenskej republike a v zahraničí, zvlášť členom etických komisií. Má za cieľ napomáhať medzinárodnú výmenu informácií a dialóg na poli medicínskej etiky a bioetiky. Prináša informácie o aktuálnych podujatiach a udalostiach v oblasti medicínskej etiky a bioetiky, pôvodné práce, prehľady, významné materiály a dokumenty, kurz pre členov etických komisií, listy redakcii a recenzie. Pôvodné vedecké a odborné práce publikované v časopise sú recenzované a musia zodpovedať obvyklým medzinárodným kritériám. Založený v roku 1994 Nadáciou Ústav medicínskej etiky a bioetiky. Počas prvých rokov existencie tvorba časopisu nadväzovala na vedecko-odborné aktivity Ústavu medicínskej etiky a bioetiky, spoločného pracoviska Inštitútu pre ďalšie vzdelávanie zdravotníckych pracovníkov (IVZ) a Lekárskej fakulty Univerzity Komenského (LF UK) v Bratislave.

Medicínska etika & bioetika - Medical Ethics & Bioethics. International, bilingual, scientific – professional journal for medical ethics and bioethics. It is devoted to the broadest medical and health care professional public in the Slovak Republic and abroad. Journal pays special attention to the informational and educational needs of ethics committees' members. It aims to foster international exchange of information and dialogue in the field of medical ethics and bioethics. The journal publishes information on actual activities and events in the field of medical ethics and bioethics, original papers, review articles, important materials and documents, continuous course for ethics committees' members, letters to the editor and book reviews. Original research and review papers published in the journal are peer-reviewed and they must abide to the usual international standards. The journal was founded in 1994 by the Institute of Medical Ethics and Bioethics Foundation. During the early years of its existence, editing of the journal was related to the scientific and professional activities of the Institute of Medical Ethics and Bioethics, the joint centre of the Institute for Postgraduate Education of Health Care Professionals (IPEHCP) and the Faculty of Medicine of the Comenius University (FM CU) in Bratislava.

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