

Bioethical Responsibility towards Current and Future Generations Foundations and Applications – Part II

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Introduction

The publication's first part on bioethical responsibility towards current and future generations¹ aimed at solidly grounding the concept of responsibility on constitutive pillars of a human person's "overall reality". For this purpose, we had systematically and critically analysed what the term of responsibility actually means and what it realistically may entail for the human person. By this means, we were then finally able to synthetically circumscribe the term of responsibility as "the human person's free 'ought to respond' to the call of the good". Starting from this "foundation stone", the present article aims at further elaborating the concrete facticity of the human person's responsibility.

The reality of love founds the person's bioethical responsibility towards current and future generations

The human being who lives in the world «necessarily finds himself living in encounter with other humans»². Even more profoundly, «being-with others and for-others belongs to the very core of human existence»³. Moreover, «this intersubjective relationship [...] is based on the very structure of the human being. Being open towards the other is a permanent state constitutive of man and regulates any action or intersubjective relationship»⁴. Since *intersubjectivity* is an essential constitutive of man⁵, it is necessarily also constitutively present in him when he is supposed to

realize responsibility. Continuing the initially quoted thought of Dietrich Bonhoeffer (ref. 2), he amends that the necessary encounter with other humans «imposes on the human person a particular responsibility for the other individual»⁶. He clearly expresses how crucial the encounter with other concrete persons is in order to be able to speak at all about someone's *real responsibility*: «At the moment, when the person takes responsibility for other humans [...], the real ethical situation occurs; this reality essentially differs from abstraction, in which the human being usually seeks to overcome ethics»⁷.

A bridge needs to be built here from the concept of intrinsic personal intersubjectivity to the previously-introduced "Absolute", which attracts and "calls" the human being (Part I). This Absolute towards which a person continuously tends in his life ultimately corresponds to God – who is "Absolute Being"⁸. In accordance with Judeo-Christian tradition, God is *personal*. Christian faith affirms a Trinitarian personal God, i.e. three persons in one God – Father, Son and Holy Spirit. In particular through the divine and human *person* of Jesus Christ, the son of God, God entered and still enters in a *personal relationship* with every human being. Speaking with the words of Pope Benedict XVI, «Being Christian is not the result of an ethical choice or a lofty idea, but the encounter with an event, a person, which gives life a new horizon and a decisive direction»⁹. Hence, the bridge to be built consists in affirming that concrete interpersonal relationships are intrinsically inherent in the human person's *entire* being.

Most importantly, the personal relationship that the Trinitarian God establishes with each human person is a relationship of *love*. «God is love, and whoever remains in love remains in God and God in him»¹⁰. As expressed by Benedict XVI, «these words from the First Letter of John express with remarkable clarity the heart of the Christian faith: the Christian image of God and the resulting image of mankind and its destiny»¹¹. He further emphasizes that «in the same verse, Saint John also offers a kind of summary of the Christian life: “We have come to know and to believe in the love God has for us”»¹². Thus, the reality of love, which is inseparably linked to knowledge, is the source and aim of every human being’s life. As affirmed by Pope Francis, «we were made for love»¹³.

The reality of love, which is sourced in God and addressed to every human being, is what essentially constitutes *the* uniting bond among humans. This is the basis on which Pope Francis rightly claims that «we need to strengthen the conviction that we are one single human family»¹⁴. Love is *the* fundament of human interdependence, which was introduced as argument to substantiate (bioethical) responsibility (Part I). Further, as emphasized by Pope Francis, the entire «creation is of the order of love. God’s love is the fundamental moving force in all created things»¹⁵. Hence, the fact that «every creature is thus the object of the Father’s tenderness»¹⁶ is the root in which the interdependence of *all* creatures is most profoundly sourced.

The initially emphasized *concreteness* of interpersonal relationship as prerequisite in order to be able to speak about *real* responsibility goes hand in hand with the *concreteness* on how this responsibility is then realized by the responsible person. In fact, «the responsible is bound to his concrete neighbour, who lives in his concrete reality»¹⁷. Consequently, as far as the responsible person is concerned, «his behaviour is not once for ever pre-defined and fixed [...]; it rather rises with the given situation. [...] He seeks to grasp and to fulfil what is necessary and due in the given situation. [...] The responsible person shall not force a foreign law on reality; on the con-

trary, his acting is in a real sense “*according reality*”»¹⁸. Bonhoeffer finally gets to the heart on how to act responsibly: «Not taking the world off its hinges, but realizing at a given place with a view at reality what is necessary – this may be the task»¹⁹.

Does this realistic way of acting responsibly not basically correspond to “the little way of love” that Therese of Lisieux taught? Are small, but realistic steps not those that really do justice to the reality of love? And is this fact not the most profound reason why responsible acting should also follow this path of small steps? In one of the final sections of his encyclical *Laudato si’* Pope Francis even recommends it as way on how to care for “our common home”²⁰. He further extends the impact of love to encompass a civic and social dimension when requiring that «“Love in social life [...] must be given renewed value, becoming the constant and highest norm for all activity”»^(a). [...] Social love moves us to devise larger strategies to halt environmental degradation and to encourage a “culture of care” which permeates all of society»²¹. His line of thought is entirely applicable on how *responsibility* is supposed to be effectively realized in society.

Pope Francis’ words clearly express the power that is inherent in love and that is ultimately able to overcome innumerable threats to which the entire creation is exposed. While Hans Jonas attributed in one of his sharp analyses such apocalyptic threats essentially to an unleashed power of knowledge, one is induced to equate precisely *love* with that generally expressed power that Hans Jonas urged as only effective remedy against these threats. Jonas’ famous claim for a “power over power”²² might indeed be interpreted in this way so that exercising the power of love over the power of destructive tendencies may characterize the human person’s real responsibility.

Translation to bioethical responsibility

The first element that occurs when translating these findings to the area of bioethical

responsibility towards current and future generations is the true understanding of “being responsible for something”. In fact, since responsibility is always intrinsically *aimed at a person*, it essentially means “being responsible for *someone*”. Consequently, «“responsibility for something” does not mean its benefit for the human being [...], but its orientation towards a person»²³. This is important when evaluating values and principles that are at stake in a specific bioethical case as they should first and foremost *serve the person*. This attitude should also guide the work of scientists, which is rather indirectly linked to concrete interpersonal relationships. In fact, whereas physicians may experience direct personal relationships with their patients, scientists who work in an analytical laboratory need to make themselves consciously aware that their bioethical responsibility refers to those persons from which they analyse test samples.

A similar attitude applies to the bioethical responsibility towards future generations; a concrete case may be monitoring of a pre-clinical or a clinical trial in order to develop a safe and efficient new medicinal product. This example evidently presupposes that scientists or health care professionals already act responsibly towards those living beings involved in these trials, i.e. animals in pre-clinical and humans in clinical studies. Beyond that, a conscious effort is required to orient their bioethical responsibility towards people who will exist and profit from these trials in future.

A second key element concerns the translation of the “little way of love” to the bioethical realm. Reference is made to the previously mentioned report on *Late lessons from early warnings* (see Part I) as well as Hans Jonas’ *Imperative of Responsibility*. Both works are penetrated by a vivid call for more scientific humility, which also means to show more respect in front of unknowns and to con-

sequently perform smaller steps forward. Is this indeed not precisely what the precautionary principle primarily consists in? Moreover, although this principle stems from the scientific area, is it not fully appropriate to identify it here with the recommended little way of love? Footsteps may in this sense reflect *decisions* that were taken – a direction of one’s way was thus chosen. In addition, the term of “way” also expresses what the precautionary principle essentially means, namely to proceed forward in one’s efforts – and not to stand still.

A third key element concerns the bioethical responsibility to protect and to preserve the human being’s *given nature*. Again, reference is made to Jonas’ *Imperative of Responsibility*, wherein he claimed that man should still exist in future *as human being*. The justified question rises here whether some of the current enhancement technologies, which aim at enhancing the human

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being’s physical and / or psychical performance, fulfil Jonas’ “first commandment”²⁵? Is it really ensured that man will exist as human being if some or even all of his constitutive limits, which might in reality make up his real strengths, are stepwise eliminated or transformed through technological inventions? In fact, «is the human being not even dependent on obstacles, detours, resistance, in order to mature»²⁶ – as human? According to Giovanni Maio, the «basic deficit within enhancement-triggered thinking consists in not acknowledging the good of being given to oneself»²⁷. Hence, it appears that, while enhancement technologies concern one specific bioethical issue that may be considered as restricted to a limited group of people, they nevertheless reveal a loss, which concerns the entire society, namely the loss of a «fundamental attitude of thankfulness»²⁸. In fact, Maio identifies precisely this loss also in conjunction with the current age of prevention²⁹. According

to him, health and life in general, do not exclusively consist in performance. As he recommends, to teach such a fundamental gratitude «could represent a new form of health care education and prevention with human face»³⁰. People would then learn to discover, appreciate and consequently protect their health and life. To rediscover and live gratitude for one's given nature undeniably expresses one's bioethical responsibility – towards oneself, towards current and also future generations.

With a view on the vast horizon of love, as it has been introduced in the previous section(s), individual “stars” may now be detected that guide the bioethicists' efforts to act responsibly. They may now comprehend that they always live in intrinsic interpersonal relationships. They may also acknowledge their personal responsibility as *free “ought to respond”*. They may now have become more strongly aware of the fact that they are always responsible for *someone*. They may recognize the invitation and duty to proceed also in their professional life via the “little way of love” by e.g. constantly preserving scientific humility particularly in front of unknowns. In this context, they may realize the high relevance of taking the given creational interdependence into consideration. Further, they can rely on the truth that real responsibility is always concrete and limited. In their striving towards a real culture of care, bioethicists may also be encouraged by the fact that real love is not a “private sentiment”, which is totally misplaced in biomedical sciences, but a powerful social reality. Even though bioethicists may not require a simple “cookbook”, which contains methods on how to act responsibly in biomedical sciences, they may nevertheless be highly interested in understanding more concretely how the gained fundamental knowledge on bioethical responsibility is effectively implemented in specific cases. The following applicative part precisely aims at addressing and illustrating this request.

Development and lifecycle of a new medicinal product for humans

The focus will be laid on one very specific and at the same time very vast sector of bioethical responsibility, namely the development of a new medicinal product for humans and its subsequent use after having been approved by health authorities for marketing. Therein, the performance of clinical trials with children, and, second, safety monitoring of medicinal products, called “pharmacovigilance” will be explicitly addressed. Beside the description of the biomedical framework, attention will be paid to the question where bioethical responsibility towards current and future generations specifically comes into play.

Performance of clinical trials with children

Experimentation on humans is concisely defined as «the systematic investigation of hypotheses and theories that is controlled by sound scientific techniques and designed to develop or contribute to generalizable knowledge»³¹. A basic ethical issue in experimentation on humans is rooted, according to Hans Jonas, in the scientific method itself, as it “*reifies* the subject to a study *object* and *exploits* him for subject-external purposes”³². Key to resolve such instrumentalisation is the informed consent that the research subject freely gives prior to any experimentation³³. In fact, «by freely consenting to experimentation, the subject makes the research purpose to his *own personal purpose*. In this way the principle of autonomy is safeguarded»³⁴.

The World Medical Association has anchored this mandatory requirement for informed consent to be freely given by research subjects in the Declaration of Helsinki; see Articles 25 and 26³⁵. The European Convention on Human Rights and Biomedicine also explicitly requires in the context of scientific research as one protective measure for research subjects their informed consent; see Article 16³⁶. In addition, the Convention firmly declares as overarching general rule for *any* application in biology and medicine that «the

interests and welfare of the human being shall prevail over the sole interest of society or science»³⁷; see Article 2.

Research subjects who are not able to consent to research, such as “minor children, many psychiatric patients, unconscious persons or dementia patients”³⁸ represent a particularly vulnerable population, which needs supplementary protection. Most importantly, «the criterion of “*minimal risk*” plays a key role as ethical prerequisite in research with children»³⁹. Hence, *beyond* the above-mentioned requirements for studies involving subjects who are able to consent, the Oviedo Convention requires in Article 17 that subjects who are not able

to consent shall only be included in studies under following supplementary conditions: «Results of the research have the potential to produce real and direct benefit to his or her health; research of comparable effectiveness cannot be carried out on individuals capable of giving consent; the necessary authorisation [by the legal representative] has been given specifically [...]; the person concerned does not object»⁴⁰.

In light of the need to improve the availability of medicines, which adequately meet the specific requirements of the paediatric population, the European Commission published in December 2006 the Paediatric Regulation, which entered into force in the European Union in January 2007⁴¹. This Regulation provided a legally binding frame for the conduct of trials in the paediatric population (i.e. children aged between birth and 18 years)⁴². Based on this regulation, the clinical development of a new medicinal product should include a mandatory paediatric investigation plan, on which the «development and authorisation of medicinal products for the paediatric population should be based»⁴³. For this purpose, a specific Paediatric Committee was established at the European Medicines Agency, EMA, essentially in order to assess, approve or reject and follow-up

submitted plans⁴⁴. One of the key aims of this regulation is to prevent that the paediatric population is subjected to “unnecessary clinical trials”⁴⁵. At the same time, it aims at facing and solving issues «resulting from the absence of suitably adapted medicinal products for the paediatric population [such as] inadequate dosage information which leads to increased risks of adverse reactions including death, ineffective treatment through under-dosage»⁴⁶.

A concrete example on how the risk is minimized for children refers to the requirements on the clinical investigation of new Factor VIII products for treatment of Haemophilia A. As described

in EMA’s respective guideline, «the clinical development [...] should follow a stepwise approach in order to have some experience in adults and older children before investigating younger children»⁴⁷. More specifically, the clinical investigation should start with previously treated patients (PTPs) aged 12 years or older, including adults. Subsequently, when pharmacokinetic (PK) and efficacy/safety data from 20 PTPs of this first age cohort are available (at least 50 exposure days, EDs), «the clinical trial(s) in children 0 - <12 years can be initiated»⁴⁸. These trials should «include at least 50 children allocated to two age cohorts. A minimum of 25 patients should be PTPs at the age of 6-<12 years and at least 25 patients should be <6 years who have undergone >50 EDs with previous factor VIII products»⁴⁹.

Clinical trials with previously untreated patients (PUPs), which realistically refer to new-borns or to babies up to approximately 2 years, can only be started «when data are available from 20 patients participating in the children trial <12 years with 50 ED each, including a minimum of 10 patients <6 years, and when pharmacokinetic investigations in children <12 years are completed»⁵⁰. Thus, the mandatory clinical investigation of new FVIII products in the paediatric population

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clearly protects through its stepwise approach the most vulnerable age cohort.

In order to evaluate whether the aims as established in the Paediatric Regulation are indeed achieved, the European Commission publishes every five years a comprehensive report based on *all* assessed relevant submissions. As stated in their five-year report published in June 2013, «there is already evidence of increased and better research, increased availability of paediatric medicines and age-appropriate information, which are filling in gaps in knowledge on paediatric medicines»⁵¹. However, efforts need to be increased. In fact, one lesson learned from this period is that «diseases that occur frequently or exclusively in children are both underrepresented and poorly addressed [in paediatric investigation plans] because the main driver of pharmaceutical research remains the adult indication and market»⁵². Overall, while the «legislative force of the Paediatric Regulation»⁵³ enabled to realize this specific responsibility towards children and towards those who will live in future, it is to be seriously hoped that specific paediatric medical needs will be even more appropriately met in the future. Striving for this aim by committing oneself as the children's "speaking tube" is undeniably a noble realization of one's bioethical responsibility.

Safety monitoring of medicinal products

Before a medicinal product is authorised to be marketed and used, the proof of its safety and efficacy is «limited to the results from clinical trials»⁵⁴, which included only «a relatively small number of patients for a limited length of time»⁵⁵. However, «some side effects or "adverse reactions" may not be seen until a very large number of people have received the medicine and used it over longer time periods. This only happens once healthcare professionals begin prescribing. It is therefore vital that the safety of all medicines is monitored throughout their use in healthcare practice»⁵⁶.

The entire safety and efficacy monitoring of a medicinal product refers to the term of pharmacovigilance. The complete European legislation on pharmacovigilance was substantially revised during several years and came into effect in July 2012. Regarding the revision's background, «the development of the pharmacovigilance legislation was based on the observation that adverse drug reactions (ADRs), 'noxious and unintended' responses to a medicine, caused around 197,000 deaths per year in the EU»⁵⁷. Due to this alarming number of yearly deaths, EMA initiated in 2005 an extensive revision on its pharmacovigilance legislation⁵⁸. Hence, in order to «reduce the number of ADRs in the EU»⁵⁹ the revised pharmacovigilance legislation requires: «The collection of better data on medicines and their safety; rapid and robust assessment of issues related to the safety of medicines; effective regulatory action to deliver safe and effective use of medicines; empowerment of patients through reporting and participation; and increased levels of transparency and better communication»⁶⁰. As far as marketing authorisation applicants and holders are concerned, the new legislation also aims to «minimise duplication of effort [...] and to establish a clear legal framework for post-authorisation monitoring»⁶¹.

In the frame of this new legislation, a specific committee was established in 2012 at EMA, which is «responsible for assessing and monitoring safety issues for human medicines»⁶². One of the new legislation's key elements is the so-called Risk Management Plan (RMP). Its submission is mandatory within new marketing authorisation applications. Overall, «the plan includes commitments on how the medicine will be monitored for safety during its lifetime, and on risk-minimisation activities»⁶³. More specifically, it should include information on: «A medicine's safety profile; how its risks will be prevented or minimised in patients; plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine; risk factors for developing adverse reactions; measuring the effectiveness of risk-minimisation measures»⁶⁴.

Particularly noteworthy is the requirement to specifically address in the RMP – beside identified and potential risks – any *missing information*, meaning «gaps in knowledge about the safety of a medicinal product for certain anticipated utilisation (e.g. long-term use) or for use in particular patient populations, for which there is insufficient knowledge to determine whether the safety profile differs from that characterised so far»⁶⁵. Based on this, applicants are also asked to present «how missing information will be sought»⁶⁶. Consequently, «RMPs are continually modified and updated throughout the lifetime of the medicine as new information becomes available»⁶⁷. More precisely, «an RMP update is expected to be submitted at any time when there is a change in [...] safety concerns, or when there is a new or a significant change in the existing additional pharmacovigilance or additional risk minimisation activities»⁶⁸.

Noteworthy is also another new pharmacovigilance tool, which particularly enables patients to enlarge their (bio)-ethical responsibility. In fact, the new «legislation introduced a right for individual European citizens to report suspected side effects of medicines directly to national medicines regulatory authorities»⁶⁹. Previously unknown signals may now be detected earlier or they may now be detected for the first time. As reported by EMA in its one-year report following implementation of the new legislation, many patients have made use of their right «with over 9,000 more patient reports received [...] in the reporting period»⁷⁰. These reports evidently need to be subsequently assessed for their validity and whether they lead to any relevant safety warnings.

Taken together, the new pharmacovigilance legislation clearly represents a framework both for individuals as well as for civil societies as a whole to increasingly take on their bioethical responsibility towards current and future generations.

Conclusion

Two representative – though not exhaustive – milestones in the development and use of a medicinal product for humans were addressed in more detail in order to visualize the connected bioethical responsibility of involved persons. While these two cases may apparently not encompass *everyone's* acting, they nevertheless illustrate a so-to-speak “universal question” on how human persons may realize

their (bio)-ethical responsibility. In fact, in the midst of contemporary biomedical and biotechnological advancements and in order to effectively do justice to all human beings, the need for guiding orientation for humans' actions rises with ever growing urgency. In-

separably linked to this search is the question what human beings actually are responsible for and, further on, how they may be able to realize their responsibilities both on a personal as well as on a communitarian level.

A “methodological triangle” consisting of (1) competences in health care or biomedical sciences, (2) ethical considerations, and (3) an anthropological fundament was applied for unfolding bioethical responsibility towards current and future generations. The chosen *interdisciplinary* approach further substantiated the extensive relevance of this topic. Finally, it is to be hoped that the present work conveys the message that real responsibility ultimately remains – as challenging as it might often be in daily life – first and foremost a precious *gift* – for us and from us.

NOTE

¹ G. KUGLER, «Bioethical Responsibility towards Current and Future Generations. Foundations and Applications – Part I», in *Studia Bioethica* vol. 10 (2017) n.3, 37-45.

² D. BONHOEFFER, *Ethik. Dietrich Bonhoeffer Werke Band 6*, Gütersloher Verlagshaus, Gütersloh 2006, 219.

The entire safety and efficacy monitoring of a medicinal product refers to the term of pharmacovigilance

Translated text: «Der Mensch lebt notwendig in einer Begegnung mit anderen Menschen, und ihm wird mit dieser Begegnung in einer je verschiedenen Form eine Verantwortung für den anderen Menschen auferlegt».

³ R. LUCAS LUCAS, *Man Incarnate Spirit – a Philosophy of Man Compendium*, Circle Press, USA 2005, 397.

⁴ R. LUCAS LUCAS, *Man Incarnate Spirit...*, 397.

⁵ Cf. *Ibid.* 266.

⁶ D. BONHOEFFER, *Ethik ...*, 219.

See endnote 1 for a translation of the original German quotation.

⁷ D. BONHOEFFER, *Ethik ...*, 220:

Translated text: «In dem Augenblick, in dem ein Mensch Verantwortung für andere Menschen auf sich nimmt, entsteht die echte ethische Situation, die sich von der Abstraktion, in der der Mensch sonst das Ethische zu bewältigen sucht, allerdings wesentlich unterscheidet».

⁸ Cf. R. LUCAS LUCAS, *Man Incarnate Spirit ...*, 325.

⁹ BENEDICT XVI, Encyclical *Deus caritas est*, 1 : AAS 98 (2005), 217. http://w2.vatican.va/content/benedict-xvi/en/encyclicals/documents/hf_ben-xvi_enc_20051225_deus-caritas-est.html (Accessed on 26th July 2017).

¹⁰ 1 Jn 4:16. Quotation from the New American Bible. http://www.vatican.va/archive/ENG0839/___P12E.HTM (Accessed on 26th July 2017).

¹¹ BENEDICT XVI, Encyclical *Deus caritas est*, 1 : AAS 98 (2005), 217.

¹² *Ibid.*

¹³ FRANCIS, Encyclical *Laudato si'*, 58: AAS 107 (2015), 870.

¹⁴ *Ibid.* 52: AAS 107 (2015), 868.

¹⁵ *Ibid.* 77: AAS 107 (2015), 877.

¹⁶ *Ibid.*

¹⁷ D. BONHOEFFER, *Ethik ...*, 260.

Translated text: «Der Verantwortliche ist an den konkreten Nächsten in seiner konkreten Wirklichkeit gewiesen. Sein Verhalten liegt nicht von vornherein und ein für allemal [...] fest [...]. Der Verantwortliche hat der Wirklichkeit nicht ein fremdes Gesetz aufzuzwingen, vielmehr ist das Handeln des Verantwortlichen im echten Sinne „wirklichkeitsgemäß“».

¹⁸ *Ibid.* 260.

See endnote 17 for the translation of the original German quotation.

¹⁹ D. BONHOEFFER, *Ethik ...*, 267.

Translated text: «Nicht die Welt aus den Angeln heben, sondern am gegebenen Ort das im Blick auf die Wirklichkeit Notwendige zu tun, kann die Aufgabe sein».

²⁰ FRANCIS, Encyclical *Laudato si'*. Reference is made to the encyclical's title, which states “on care for our common home.

²¹ FRANCIS, Encyclical *Laudato si'*, 231: AAS 107 (2015), 937-938.

Therein, reference ^(a) corresponds to reference ^(b) Pontifical Council for Justice and Peace, *Compendium of the Social Doctrine of the Church*, 582.

²² Cf. H. JONAS, *The Imperative of Responsibility ...*, 141.

²³ D. BONHOEFFER, *Ethik ...*, 259.

Translated text: «Nicht der Nutzen der Sache für den Menschen [...], sondern ihre wesenhafte Ausrichtung auf den Menschen ist unter “Verantwortung für eine Sache” zu verstehen».

²⁴ Cf. H. JONAS, *The Imperative of Responsibility ...*, 139.

²⁵ Cf. *Ibid.*

²⁶ G. MAIO, *Mittelpunkt Mensch: Ethik in der Medizin*, Schattauer, Stuttgart 2012, 326.

Translated text: «[Hier muß man jedoch fragen,] ob der Mensch nicht sogar angewiesen ist auf Hürden, auf Umwege, auf Widerstände, um reifen zu können».

²⁷ G. MAIO, *Mittelpunkt Mensch: Ethik in der Medizin ...*, 332.

Translated text: «Das Nicht-Anerkennen des Guten im Gegebenen ist das Grunddefizit einer an Enhancement-Maßnahmen orientierten Denkweise».

²⁸ G. MAIO, «The limits of self-responsibility in the age of prevention», in J. BONELLI, F. KUMMER, E. PRAT, (ed.), *Lifestyle and Responsibility*, Imago Hominis 18 (3), 171-178.

Translated text: «[Statt dieser exzessiven Erwartungshaltung an das eigene Leben, an das eigene Glück, erscheint es notwendiger denn je, den Menschen neu beizubringen, etwas wiederzuentdecken], was heute vollkommen verlustig gegangen ist, nämlich die Grundhaltung der Dankbarkeit”. Und genau hier könnte eine neue Form von Gesundheitserziehung und Prävention mit humanem Antlitz starten».

²⁹ Cf. *Ibid.*

See endnote 28 for the translation of the original German quotation.

³⁰ *Ibid.*

See endnote 27 for the translation of the original German quotation.

³¹ T.L. BEAUCHAMP, «The intersection of research and practice», in: A. GOLDWORTH (ed.): *Ethics and Perinatology*. Oxford University Press, New York 1995, 231-244.

³² Cf. H. JONAS, «Philosophical reflections on experimenting with human subjects», *Daedalus* 1969, 98 (2), 219-247.

³³ Cf. G. MAIO, *Mittelpunkt Mensch: Ethik in der Medizin...*, 299.

Translated text: «Das ethische Problem der Forschung am Menschen dreht sich also um die Frage, wie diese Momente illegitimer Versachlichung und Verzweckung aufgehoben werden können. Genau hier greift das Instrument der Einwilligung nach Aufklärung. Dies zur zentralen Forderung zu machen, ist ethisch damit zu begründen, dass die Versuchsperson mit der freien Einwilligung in einen Versuch den Zweck des Versuchs zu ihrem eigenen Zweck macht».

³⁴ *Ibid.* Emphasis in italic added.

See endnote 33 for the original German quotation.

³⁵ WMA. *Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects*, 64th WMA General Assembly, Fortaleza, Brazil, October 2013. <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/> (Accessed on 26th July 2017).

³⁶ COUNCIL OF EUROPE. *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine*, Oviedo, 4th June 1997. <https://rm.coe.int/CoERMPublicCommonSearchServices/DisplayDCTMContent?documentId=090000168007cf98> (Accessed on 26th July 2017).

³⁷ *Ibid.*

³⁸ Cf. G. MAIO, *Mittelpunkt Mensch: Ethik in der Medizin...*, 301:

Translated text: «Zu [nicht einwilligungsfähigen Patienten] zählen beispielsweise viele psychiatrische Patienten, aber auch Kinder, Bewusstlose und Demenz-Patienten».

³⁹ G. MAIO, *Mittelpunkt Mensch: Ethik in der Medizin...*, 304. Emphasis in bold and italic added.

Translated text: «Daher spielt das Kriterium des »minimalen Risikos« als ethische Voraussetzung der Forschung mit Kindern eine große Rolle».

⁴⁰ COUNCIL OF EUROPE, *Convention on Human Rights and Biomedicine*.

The requirement for the authorisation by the legal representative is stated in Article 6 of the Convention.

⁴¹ THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION. *Regulation (EC) No 1901/2006 on medicinal products for paediatric use*, 27th December 2006.

http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf (Accessed on 26th July 2017).

⁴² *Paediatric Regulation ...*, Chapter 1, Article 2.

⁴³ *Ibid.* Preamble (9).

⁴⁴ *Ibid.* Chapter 2, Article 3.

⁴⁵ *Ibid.* Preamble (3).

⁴⁶ *Ibid.* Preamble (3).

⁴⁷ COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP), *Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products*, EMA/CHMP/BPWP/14453/2009 rev.1, 8.

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/02/WC500201773.pdf (Accessed on 26th July 2017).

⁴⁸ *Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products ...*, 8.

⁴⁹ *Ibid.*, 12.

⁵⁰ *Ibid.*, 13.

⁵¹ EUROPEAN MEDICINES AGENCY (EMA), *5-year Report to the European Commission. General report on the experience acquired as a result of the application of the Paediatric Regulation*, EMA/428172/2012, 41.

http://ec.europa.eu/health/sites/health/files/files/paediatrics/2012-09_pediatic_report-annex1-2_en.pdf (Accessed on 26th July 2017).

⁵² *5-year Report to the European Commission. General report on the experience acquired as a result of the application of the Paediatric Regulation*, 42.

⁵³ *Ibid.*

⁵⁴ EUROPEAN MEDICINES AGENCY (EMA), *Safety monitoring of medicines*, http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000456.jsp&mid=WC0b01ac05801ae8fb (Accessed on 26th July 2017).

⁵⁵ EMA, *Safety monitoring of medicines*.

⁵⁶ *Ibid.*

⁵⁷ EUROPEAN MEDICINES AGENCY (EMA), *Pharmacovigilance legislation*, http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000491.jsp&mid=WC0b01ac058058f32d (Accessed on 26th July 2017).

⁵⁸ Cf. EMA, *Pharmacovigilance legislation*.

⁵⁹ *Ibid.*

⁶⁰ *Ibid.*

⁶¹ *Ibid.*

⁶² EMA, *Safety monitoring of medicines*.

⁶³ EUROPEAN MEDICINES AGENCY (EMA), *One-year report on human medicines pharmacovigilance tasks of the European Medicines Agency*.

Reporting period: 2 July 2012 to 1 July 2013, EMA/171322/2014 Corr, 25.

http://ec.europa.eu/health/sites/health/files/files/pharmacovigilance/2014_ema_oneyear_pharmacov_en.pdf (Accessed on 26th July 2017).

⁶⁴ EUROPEAN MEDICINES AGENCY (EMA), *Risk-management plans*, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000360.jsp&mid=WC0b01ac058067a113 (Accessed on 26th July 2017).

⁶⁵ EUROPEAN MEDICINES AGENCY (EMA), *Guideline on good pharmacovigilance practices (GVP). Module V – Risk management systems (Rev 2)*, EMA/838713/2011 Rev 2, 6. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf (Accessed on 26th July 2017).

⁶⁶ EMA, *Guideline on good pharmacovigilance practices (GVP). Module V – Risk management systems (Rev 2)*, 19.

⁶⁷ EMA, *Risk-management plans*.

⁶⁸ EMA, *Guideline on good pharmacovigilance practices (GVP). Module V – Risk management systems (Rev 2)*, 34.

⁶⁹ EMA, *One-year report on human medicines pharmacovigilance tasks of the European Medicines Agency. Reporting period: 2 July 2012 to 1 July 2013*, 29. http://ec.europa.eu/health/sites/health/files/files/pharmacovigilance/2014_ema_oneyear_pharmacov_en.pdf (Accessed on 26th July 2017).

⁷⁰ EMA, *One-year report on human medicines pharmacovigilance tasks of the European Medicines Agency ...*, 4.