PRESIDENZA DEL CONSIGLIO DEI MINISTRI

SEGRETARIATO GENERALE

N. 9



Italian National Bioethics Committee

Opinions 2015 - 2016

ISBN 978-88-9088-205-0

Presidenza del Consiglio dei Ministri

DIPARTIMENTO PER L'INFORMAZIONE E L'EDITORIA

Presidenza del Consiglio dei Ministri

SEGRETARIATO GENERALE
Comitato Nazionale per la Bioetica

OPINIONS
2015-2016

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A special thanks to Domizia Di Maggio, Dorothea Karic, Andrea Giulia Melchionna and Nicolò Messina for the precious and generous collaboration.

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Presidenza del Consiglio dei Ministri



SINGLE PATIENT CARE AND NON-VALIDATED TREATMENTS (THE SO-CALLED "COMPASSIONATE USE")

ACCOMPANIED BY A JURIDICAL NOTE

27 February 2015

Presentation

In this document the Committee deals with the issue of therapeutic treatments not validated by regulatory authorities, inserting a further step in the analysis of the different profiles of the right to health, from freedom of care to informed consent, and to the doctor-patient relationship.

In particular, the use of theoretically validated products, whose effectiveness and safety for a specific use has not yet been verified, it has already been dealt with marginally by the Committee, in 1998, in a brief "reply" to the Ethics Committee of the National Institute for Cancer Research in relation to the so-called "Di Bella case". This was an alternative therapy for the treatment of tumours which required a plurality of *off-label* drugs, that are used for indications, dosages or methods other than those for which they had been authorized. The combination therapy had no scientific basis and was defined as "recourse to impromptu prescription" by the same Law no. 94/1998 that the legislature had enacted, under the pressure of public opinion and a number of court actions, in order to carry out experimental verification of its claimed therapeutic capacities.

After several years the so-called "Stamina case" has revived the same problems: inadequacy of a scientific basis, public pressure, intervention of judges, impromptu regulatory measures to allow controlled trials. Unlike the "Di Bella case" in the latter matter the combined application of already studied drugs was not called into question, but even the use on individual patients of a not yet approved and largely unknown treatment.

This document only draws inspiration from this incident, for which the judicial process has not yet been completed at the time of writing of this opinion. It seems clear that the problem of the administration of non-validated treatments for compassionate use has a specific and independent bioethical relevance for far more complex reasons than those in the Italian "cases", as attested by art. 37 of the Declaration of Helsinki, art. 83 of EC Regulation no. 726/2004, art. 13 of the Code of Medical Ethics and the laws of different countries on treatments on an individual basis, special access programs, unproven interventions in clinical practice, programs of difficult cases, exceptions for humanitarian use.

The first part of the document describes, therefore, this general reference framework, and then examines the individual profiles from three dif-

ferent points of view: that of the patient, the doctor and the institutions. A very precise choice made by the Committee, who wanted to highlight the variety of needs, experiences and - very often - tensions that arise in these circumstances.

The different perspectives, often do not coincide in the expectations, demands and needs of all parties involved, however, they have allowed us to outline with precision the boundaries within which so-called "compassionate treatments" can be administered, without questioning the consolidated methods of clinical trials, rather, on the contrary, using as a constant reference point and ultimate horizon precisely those regulatory criteria that the medical and scientific community and public institutions share internationally.

The Committee hopes, first of all, that a different expression can be found for "compassionate care", so as not to be confused with legitimate feelings of empathy towards those who are seriously and incurably ill. The alternate proposal is "non-validated treatments for personal and non-repetitive use", with the hope that an international "*consensus conference*" can promote its use. Access to these treatments should be exceptional, and only in the absence of validated therapies, in cases of extreme urgency and emergency for patients with a life threatening condition, and such treatments can never be an explicit or surreptitious alternative to clinical experimentation. They must have a reasonable and sound scientific basis: data published in international *peer-reviewed* journals, with robust scientific evidence at least on animal models and preferably with the results of phase I clinical trials. The prescription must be the responsibility of a panel of experts, appointed by public health institutions, in conditions of total transparency, absence of conflicts of interest, with publication of both the composition of the products as well as the results of treatment, comprehensive explanation to patients about the potential dangers of non-validated treatments, the cost of drugs borne by the manufacturers and monitoring carried out by public health institutions. Only under these conditions compassionate treatment can be considered ethically licit and be included in the general right to health care.

The opinion is supplemented by a detailed legal note, particularly useful given the complexity and fragmented nature of the relevant regulatory framework.

The Working Group was coordinated by Prof. Salvatore Amato and Prof. Assuntina Morresi.

Prof. Lorenzo d'Avack played a central role in the reconsideration of several of the most complex and delicate paragraphs, and in the reworking of the legal note. Prof. Stefano Canestrari, Prof. Carlo Casonato and Dr. Carlo Petrini also contributed to the juridical note.

Prof. Silvio Garattini has revised and made several integrations to the text, which has benefitted from his essential and effective style and scientific expertise.

Notations or written interventions were also received from: Prof. Antonio Da Re, Prof. Paola Frati, Prof. Marianna Gensabella, Prof. Demetrio Neri, Prof. Andrea Nicolussi, and Prof. Grazia Zuffa.

The opinion was approved with 17 votes in favor (Amato, Battaglia, Caltagirone, Canestrari, Casonato, D'Agostino, d' Avack, Da Re, Di Segni, Garattini, Gensabella, Morresi, Nicolussi, Palazzani, Proietti, Sargiacomo, Toraldo) and 2 against (Flamigni and Neri), with no abstentions.

3 consultative members (Bernasconi, Conte, Petrini) also expressed a favorable opinion.

Prof. Bruno Dallapiccola, Prof. Lucetta Scaraffia, Prof. Giancarlo Umani Ronchi, Prof. Grazia Zuffa were absent and later forwarded their expressions of approval.

1. Premise

It is often specific cases which determine the bioethics agenda of a country. In Italy, the debate on freedom of treatment and on so-called compassionate treatments has taken on particular importance as a result of facts known to the public such as the cases of "Di Bella" and "Stamina". As a preliminary point, the National Committee for Bioethics (henceforth ICB or Committee) clarifies that this document, although it cannot but take account of what happened, it does not intend to enter into the merits of these specific events. We propose, rather, to examine the bioethical aspects related to the cases in question, namely freedom of treatment, informed consent, and so-called compassionate treatment, with the aim of identifying problems and to articulate, in this particularly sensitive context, criteria and paths to draw to the attention of both institutions and the health professions and, more generally, with regard to public debate.

Within this debate it must be emphasized that medicine, like any other scientific activity, has an essentially paradigmatic (*evidence-based*) nature focused on empirical verifiability *(organized scepticism)*, on shared communication and community and disinterestedness[1].

It is based, therefore, on the ethical pledge to respect for methodologically consolidated rules[2] so that the protection of health is committed to continual review and objective clinical findings for the treatments made available to patients.

Industrialization, namely continuous manufacturing, and generalized and undifferentiated marketing, which concerns the majority of currently

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[1] "Communalism, universalism, disinterestedness, organized scepticism" are the principles set out by Robert K. Merton in the second half of the twentieth century in *Teoria e struttura sociale*, Il Mulino, Bologna 1959.

[2] The ICB has repeatedly stressed these concepts. For example in the document on *Alternative Medicines and the Problem of Informed Consent*, March 18, 2005, it states significantly that "Scientific medicine, since the adoption of the experimental method, is based on the entirety of knowledge related to the structure and functions of the human body that can be developed through the interaction and integration of various methodologically based disciplines such as physics, chemistry, biology and in particular molecular biology, genetics, physiology, anatomy, general pathology, and psychology. This medicine, which day by day increases its knowledge thanks to the research of many scholars, also deserves to be called scientific for it is able, thanks to a public debate which in principle excludes all sectarianism and every esotericism, to correct itself and modify its concepts and practices with great flexibility, based on the experience of mistakes made and the development of always new paradigms".

available drugs[3], are rigidly bound to compliance with these procedures. Connected to the scientific profile and the economic one of industrial production and marketing is the legal regulation of patents which on the one hand ensures the innovativeness and plausibility of the products used and on the other affects the costs and methods of utilization.

Most countries felt, in recent years, the need to include the administration of drugs or other therapeutic treatments even in the absence of approval of regulatory authorities in various ways:

- *off-label* treatment, which defines the instructions for use, methods or dosages other than those authorized, but for which there is sound scientific basis of efficiency and tolerability;
- compassionate treatment, which defines the use of a drug, not yet authorized, for a single patient (or group of patients).

It is not intended, thereby, to question the traditional criteria for experimentation and use of drugs or therapy, but it allows, exceptionally and on the basis of a medical prescription, to resort to methods of treatment not yet approved by the regulatory authority when the patient is diagnosed with a serious disease, for which there is no validated treatment, or when available treatments have not been effective. Treatments are considered to be effective not only when they lead to a recovery but also when they lead to a better quality of life, relieving suffering and improving the overall condition of the patient. In these cases we are moving, in fact, within the grey area of a scientific validation process that has been started, but has not yet been completed, it is plausible, but not totally verified, with a rationale set forth in the literature of the sector, but not ascertained through the completion of the process that leads to marketing authorization. Situations that find their justification in their appearing to be the only, albeit uncertain, resource remaining in order to try to save a life, prolong it or improve its quality.

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[3] Art. 68 of the Legislative Decree of the 10th February 2005 no. 30, allows for the so-called Galenic exception, that allows the pharmacist, on an occasional basis and for proven therapeutic reasons, to prepare and sell in individual units a drug with a different dosage or different excipient than that put on the market, subject to medical prescription (masterful Galenic preparation) or to make it up directly with or without prescription (Galenic officinal preparation) for a particular patient. These must, in any case, be active ingredients described in the pharmacopoeia of European Union countries or contained in drugs that have been authorized for sale.

To understand the diffusion of this phenomenon we have to keep in mind the emergence of several factors. Firstly, the rapid evolution of scientific developments creates, at times, an irremovable gap between the normal course of proper experimental verification and the urgency of individual expectations. This phase disparity could condition the choices made by doctors – who are divided between the strict application of established protocols and the desire not to deny any opportunity to those suffering - and affect the way in which the patient and family members deal with the disease, often causing them to pursue any supposed therapeutic promise, seen to be indispensable, given that *evidence-based* medicine is unable to provide answers[4]. Paradoxically, it is the confidence in a science capable of dealing with any disease to foster the search for a cure at all costs, even beyond the dictates of science itself. In the United States an appropriate expression is used, *quackery products*, which corresponds to our charlatan, to indicate all *unproven medications* widely used, but whose safety and effectiveness is not recognized by the FDA[5].

This incongruity weigh even on institutions with the difficult balance between the duty to avoid occult, improper or illusory experimentation and sensitivity to the desperation not only of the patients but also of family members, who want to leave no stone unturned to save their loved ones, or at least alleviate their suffering. This discrepancy makes increasingly urgent

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[4] The International Society for Stem Cell Research in the *Guidelines for the Clinical Translation of Stem Cells* of the 3rd December 2008, focuses in particular "about the potential physical, psychological, and financial harm to patients who pursued as unproven stem cell-based" therapies "and the general lack of scientific transparency and professional accountability of those engaged in these activities". Indeed, in recent years a number of companies have arisen, which, supported by internet websites and displaying the enthusiastic testimonies of patients, promising cures for incurable diseases according to *evidence-based* medicine. "…Some laboratories promise heaven and earth to desperate patients and their relatives, who undertake sometimes costly and unnecessary 'journeys of hope'. This way of operating is dishonest, although sometimes it is carried out with good intentions, for an essentially consolatory purpose", in E. BONCINELLI, *Genetica e guarigione*, Einaudi, Torino 2014, p. 81, e-book version. As for the profound and concerning nature of this phenomenon, see C. T. SCOTT *et al., The Language of Hope: Therapeutic Intent in Stem Cell Clinical Trials,* in "The American Journal of Bioethics Primary Research", 2010, 1 (3), pp. 4-11; C. E. MURDOCH and C. T. SCOTT, *Stem Cell Tourism and the Power of Hope,* in "The American Journal of Bioethics Primary Research", 2010, 10 (5), pp. 16-23.

[5] W. S. PRAY, *Nonprescription Medications and Self-Care: Ethical, Scientific, and Educational Concerns with Unproven Medications*, in "American Journal of Pharmaceutical Education", 2006, 70 (6), pp. 1 *et seq.*

the problem of giving serious reflection to the nature and deontological limits of scientific information[6].

We cannot neglect the fact that we find ourselves faced with one of the many expressions of the need for personalized medicine in order to attenuate, under certain conditions and in certain circumstances, the rigid paths of protocol procedures, fundamental in the overall assessment of the effectiveness of drugs and therapies.

Not all situations can be standardized and the relationship between the patient and the doctor cannot be traced back to the repetitiveness of similar cases.

No doctor can easily resign himself to the inevitability of what has already happened, in particular before the difference (or the supposed difference) between the attested evaluation of prevailing scientific opinion and the benefits claimed in practice by the patient. It is not easy to ask a patient to give up pursuing even the slightest chance of life or alleged well-being, despite the lack of demonstrated evidence regarding effectiveness at the time of treatment and without there even being any confirmation in consolidated scientific knowledge.

Moreover, the time and costs, that the regulated paths of trials require for permission to commercialize a new drug, cause certain diseases, especially rare ones, not to become the subject of research by pharmaceutical companies. Often the incentive policies towards orphan drugs (see the ICB Opinion 25 November 2011 on *Orphan drugs for persons affected by rare diseases*) are inconclusive due to insufficient economic resources to be implemented. For most of these diseases, therefore, health systems are not able to offer treatment paths or even just treatments for improving the quality of life; in addition there is a lack of suitable experts for these patients, and that diseases like this frequently require the presence of several specialists (ranging from a cardiologist a neurologist, a physiotherapist, to a nutritionist).

An overall picture emerges in which families often are the ones who pull the strings of the treatment paths and healthcare of their loved ones,

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[6] For example in Italy, in the "Stamina" case, and before that in the "Di Bella" case, the media had and have a serious responsibility in fuelling expectations and illusions, often aiming more for the pursuit of sensationalism than for accurate information on the quality of the scientific data available.

they become experienced and competent in many aspects of the disease that has affected them, this is especially true if the patient is a child, as unfortunately happens in many cases. They are obviously highly motivated families who are fighting against time while waiting for something new from scholars. These families often take an active part in the search for new paths to experiment, thanks to the web that allows direct and easier contact with other patients in the same conditions, as well as with specialists and scientists in that field. Families who therefore ask forcefully and with knowledge of the facts to experiment barely glimpsed or hypothesized paths.

Behind the need to expand some of the limitations normally foreseen for pharmacological and therapeutic experimentation we therefore see the emergence of expectations, hopes, illusions that, in extreme cases in which the patient's life is at stake, fuel strong tensions.

To what extent is it possible to derogate from scientific parameters, and remain within scientific horizons? How far can the wishes of the patient be fulfilled, without creating false illusions? In the perspective of healthcare institutions, to what extent can the "compassionate" approach justify the fact that means and resources are taken from recognized treatments? To what extent can the use of non-validated therapies be left to the unquestionable judgment of the individual doctor, with the possible backing of a judge? What is the relationship between the right to health and freedom of treatment? Does patient self-determination also involve the risk of experimenting on oneself treatments that are of unknown harmfulness?[7]

Bioethical culture generally tends to encompass all of these issues

[7] These questions have also been reflected in international declarations. Art. 37 of the Declaration of Helsinki (updated in October 2013) provides for the possibility of "unproven interventions in clinical practice". It allows the use, under the responsibility of the doctor and with the consent of the patient or his legal representative, of "an unproven intervention", when there are no proven treatments or other known interventions have proved ineffective, and after seeking expert opinion on the subject. The doctor must be convinced that this drug could "constitute a hope to save the life, restore the physical integrity or alleviate the suffering of the patient". The article adds that "this intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy". In all cases, new information should be recorded and made publicly available when appropriate." In one of the many drafts of the Universal Declaration "*on Bioethics and Human Rights*" of UNESCO, art. 16 of *Scientific and Rational Method*, after pointing out that every decision and practice should be based on the best scientific information available, stressed that (v) "be considered individually, allowing for the possibility of exceptions to general rules and practices". The article was then removed from the final version, but it is the sign of a debate within the international community itself.

through expression full of emotional echoes, "compassionate use"[8] of drugs, derived from the English *compassionate use*: a vague and imprecise formula, reserved for situations very different from each other.[9]

The ICB agrees about the need to amend the term "compassionate care" and replace it with a more effective and more appropriate term to express the concept of "non-validated therapy", which at the same time avoids confusing this particular type of treatment path with a legitimate empathy for patients with severe and fatal illnesses, who are often children.

The Committee suggests the usage, for these cases, of an alternative expression: "non-validated treatments for personal and non-repetitive use"; in this formulation the emphasis is placed on the fact that treatments are not yet validated, although one can draw from a significant set of data derived from international scientific literature and reasonable scientific evidence to justify the assumption that such treatments can be validated (but of course there is no certainty that this will then actually occur). Since the ICB is aware of the difficulties of replacing a synthetic expression and corresponding to a literal translation of the original definition in the English language *compassionate use*, it suggests the creation of an International *consensus conference* to reflect on this specific issue.

Precisely because of the difficulties mentioned above, and so as to avoid misunderstandings, the adjective "compassionate" will still be used in the rest of the document.

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[8] In international literature there are also "treatments on a named-patient basis" and "special access programs", "unproven interventions in clinical practice", "temporary authorizations for use", "programs on difficult cases", "exceptions for humanitarian use", "non-repetitive use of advanced therapies". Each of these definitions reflects a different possible interpretation of a phenomenon that is as difficult to curb as it is to define within univocal patterns. Even our legislation utilizes a wide range for variations in terminology which now reflect the tensions of the moment - "use of extemporaneous prescription" (Di Bella therapy) - currently affect various aspects of the phenomenon: "use of drugs for indications other than those authorized", "use of drugs outside of clinical trials", "prescriptions for indications not provided for by the technical information or not yet authorized for the market." The attached note explains in detail the use of treatments and medication for "compassionate use", within the current legal framework.

[9] Sometimes it is suggested to reserve the term "compassionate use" only in situations where the administration of not yet commercialized drugs occurs for groups of patients and under the control of an institutionally appointed body responsible for scientific experimentation, using instead "Treatment on a named-patient basis" or "Special access programs" (SAPs), to describe the prescription of *off-label* drugs or drugs not yet authorized for individual patients and under the responsibility of individual medical institutions.

2. Bioethical profile

Even the terminological difficulties are the inevitable consequence of the extreme variety of situations before which we stand: the right to health is understood in an increasingly broader sense so that, in addition to including the quality of life, it extends to the expectations and life expectancy stretching to, in extreme cases of incurable diseases, a need for "compassion" that encompasses everything that can possibly be done "To alleviate not only physical injury but, if you will, also the patient's existential injury"[10], in order to be able to at least alleviate his conditions, while not being able to hope for any recovery. The crucial point of this placement of health within the protection of the spheres of freedom is constituted by the problem of freedom of treatment.

Freedom of treatment is an aspect of the right to health, but is not the main content of this right, because healthcare assistance requires regulation and coordination of functions and services, which cannot be entrusted entirely to individual choice. The prescription of a drug within the National Health Service (NHS) always involves the monitoring of the modalities of its administration and an evaluation on justice in the allocation of resources. A complex process that moves from each individual, but which goes much further, involving the entire health care organization.

It is different when we prescind from the NHS but the prescription takes place equally under medical supervision, as in some forms of "alternative medicine" on which the ICB has expressed itself in the previously quoted opinion *on Alternative medicines and the problem of informed consent,* with reference to "practices whose effectiveness have not been established by the criteria adopted in scientific medicine" (an expression similar to that of compassionate treatments, considering that in these efficacy is not "proven", de-

[10] "The principle that the right to health has in our legal system is extracted from these considerations, a certainly broader dimension than that which merely derives from the right to treatment or healthcare in the traditional sense of appropriate therapeutic measures to wipe out the disease or to stop its evolution. On the contrary, the necessary reference to the protection of human dignity, allows for consideration that the health conditions which are subject of constitutional provision coincide not only with the preparing of means to heal the affected person but also with whatever else may be used to alleviate not only the patient's physical injury, but if you will, also the existential one, or at least whatever may be of real utility in alleviating the functional limitations albeit without any appreciable results regarding the possible regression of the disease" (Court of Cassation, June 18, 2012, n. 9969).

spite being "ascertainable"). The ICB has reiterated, in this document, the general principle by which, notwithstanding the responsibility of the doctor in the administration of any therapeutic treatment, at the express and conscious request of the patient and in specific cases, the administration of scientifically non-validated products is justified, provided that they are not charged to the NHS and however always used as a last resort or in the absence of validated alternatives and risks being ascertained for the patient[11].

In general, if interventions not approved in clinical practice are requested, the argument often put forward is that it is one aspect of the freedom of treatment, this "claim" or "expected" aspect, expresses the demand, by the patient, to receive treatment not yet validated by the scientific community, but for which the available data portends the possibility that it may be of benefit. In other words, faced with the declared powerlessness of *evidence-based* medicine, the patient raises the question of his being "free" to look elsewhere for a cure at all cost, thus giving priority to his autonomy.

The other side of the freedom of treatment is the refusal of medical treatment, which has been dealt with in a previous ICB document (*Conscious refusal and renunciation of healthcare in the patient-doctor relationship* 24 October 2008), examining in particular the issue of the right to refuse treatment, in its broadest sense to choose the method of treatment, or not to be treated at all, and the role of the doctor whether during the renunciation or the refusal of treatment the active role of the doctor were to be requested. In that opinion, the ICB highlighted that "in current medical ethics, informed consent has taken on a key role, allowing full valorisation of the choices made by the competent patient, according to the principle of autonomy", and reiterated that: "when, in the case of a competent patient in conditions of dependence, the renunciation of treatment requires, in order to be satisfied, the active behaviour of a doctor, the doctor's right to abstain from behaviour deemed contrary to his conception of ethics and profession-

[11] The Court of Cassation (20 May 4 September 2014, n.18676) reiterated that the right to health is not susceptible to weakening. The patient has, therefore, a right to obtain timely care free of charge, even if it is not recognized by the National Health Service. However, these services must respect the principles of "appropriateness" and effectiveness of the drug or therapy within the parameters set by law. A careful comparison is necessary "between the positive results of health care and the possible negative effects of the therapy itself on the living condition of the patient".

alism is recognized. A large majority of the ICB considered that patients have in any case the right to attain alternatively the fulfillment of their request for the interruption of treatment, even in consideration of the possible abstention of the doctor or medical team".

In understanding the problem of compassionate treatment some misunderstanding may arise, in particular if one proceeds in the perspective of a general statement of freedom of treatment (or generic therapeutic self-determination). Instead, one must take into account certain distinctions. For example, the refusal of medical treatment is not based on the principle of freedom in a general sense, but on the protection of the physical and mental freedom of the individual whose bodily dimension must be respected. The request for special treatment is, however, a request for medical intervention, which, as such, operates according to the criteria of professional appropriateness and conscience. The dividing line, although controversial and problematic, between appropriate and inappropriate treatments defines medical practice and takes on a very particular importance precisely when the treatment requested is not in compliance with normal medical and scientific standards. Consequently, defining the dividing line between permissible and impermissible compassionate treatments is necessary not only for the sustainability of the NHS, an already decisive issue at least in terms of the availability of resources, but also for the autonomy and professional responsibility of those working in the healthcare sector. It then becomes a crucial problem whether, in the event of a fatal diagnosis and the absence of validated therapies, both for treatment and improvement of the quality of life, the "best interests" of the patient can be configured by a course of treatment not validated according to the shared criteria of the scientific community, which therefore could not even have been verified in terms of harmfulness to the actual patient. The ICB intends to analyze this problem from three points of view - that of the patient, the doctor, and the institutions – in order to try to highlight the variety of tensions that arise within the different standpoints that do not always fully coincide.

3. On the side of the patient

1. The patient's right to treatment and therefore to the protection of health, is first and foremost, the right to receive treatment approved after rigorous experimentation according to the methodological and ethical crite-

ria shared by the scientific community and regulated by the legal system. In this context the NHS in the dispensing of medicines and medical treatment carries out a dual role of recognition of compliance with the parameters set by the law and monitoring of the adequacy of expenditure in relation to individual needs and the interests of the community. This paragraph deals with the legal aspect of the conduct of conscious and properly informed patients, who at their own responsibility undergo treatment that has not been validated. The following paragraphs examine the issue of the right to obtain this treatment on the NHS and the role of the doctor.

The basic rule is that the administering of non-validated treatments should take place only as a well-motivated and strictly monitored exception, their sole raison d'être occurs when faced with a life threatening situation or the particularly serious nature of a disease, there being no recognised effective alternative for treatment and improvement of the quality of life of the patient in order to prevent deterioration.

In the context of compassionate care the patient's request to use a drug that has not been registered and to evade the authorization procedure established by the regulatory authorities, is characterized by the fact that the procedure has not been completed or even begun on human beings. It is therefore a matter of waiting for the patients[12]. Undoubtedly, in general it is wrong to think of "saving time" by replacing the rigor of the trials of the authorization procedures with the anecdotal attempts of compassionate use.

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[12] See the case known as "Lorenzo's Oil", where the parents themselves obtained the substances to be administered to the child and where it is clearly evident that time is life for the patient: "Suddenly it was clear as day: we were running on parallel but completely different tracks, as if research for science was one thing, but our fight for life was another. As if we were in the real world and they were in their world of abstract solutions, and the two worlds, separated by a thick sheet of glass, were unable to communicate. During the very days of the conference Lorenzo had stopped walking completely, he no longer spoke and had started having big problems swallowing saliva, which had to be sucked through a tube of plastic similar to those used by dentists. It kept going through my head that phrase used by Rizzo: 'Maybe triglyceride would be suitable, but I would not know where to find it...'. A surge of anger took hold of me and took the form of a bitter question: Were they trying to win the Nobel Prize while I was witnessing the death of my son?" in A. ODONE, *Lorenzo's Oil. A love story*, Milano 2011, pp. 62- 63. "This position is sometimes misunderstood and seen as controversial. Some have accused me of wanting to hurry up the progress of science; science, they said, should follow its own pace. For me it was nonsense. But I discovered that it is not easy to change the mindset that has always existed in the field of science, often closed to the outside world. We could not accept the idea of research which adopted the slow pace scientists were accustomed to.", *Ivi*, p. 91.

Moreover, in the context of these events there is no intention to replace rigorous scientific experiments with compassionate use, but rather to complement new attempts for treatment to due experimentation. These attempts should not be conceived as being "outside" of scientific experimentation, but "alongside" it, as anecdotal cases which however do not interfere with the trials, but accompany them not usually but only in exceptional cases and with carefully defined methods.

We can configure at least two situations. The first, in which the patient might have access to a treatment path for which experimentation on humans has already begun, and for which at least phase I has been completed. The second, in which no trials on human beings have begun.

In the first case, that is, with evidence of no harmfulness, the patient could have access to "compassionate care". It is therefore possible that in the course of a clinical trial, the drug, within highly specific conditions, may be utilized prior to being approved as a compassionate treatment. This would be a form of early access, extended to the sick in exceptional circumstances still to be accurately established, and which should however take place in a strictly controlled manner, both by the relevant authorities through the treating physicians, and also possibly by patient associations. In this way, it could give rise more easily to a virtuous circle of information regarding the entire community of patients suffering from the same disease. An early access, but with established criteria[13]: the purpose would be to speed up access for patients who do not have an alternative, when the trial has already concluded phase I and therefore there has been recognition of drug tolerability so as to justify continuation.

The most problematic situation is undoubtedly the second, which usually occurs for rare diseases, for which there is no regular experimentation in progress or a reasonably foreseeable one in the near future, because it is too costly for pharmaceutical companies, considering the small number of sufferers. The problem arises when the patient in this situation consciously requests a therapy for which the absence of harmfulness is unknown and the patient who is not able to access the therapy autonomously, requires medical intervention.

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[13] As required by the Ministerial Decree of 2003 with expenses charged to the manufacturer of the drug. The Decree currently limits recourse to the existence of a "life-threatening" condition and with phase III drugs.

The most common case can be, for example, the one concerning rare diseases for which there is reviewed scientific literature, but it is limited to some experiments on animals (see the already cited case "Lorenzo's Oil"); or, as it is increasingly occurring with the "journeys of hope" for cellular therapies in the case of fatal diseases: the patient is not able to independently access this path even when, in autologous transplantation, the patient personally provides the biological material, because the intervention of lab technicians and doctors are needed[14].

In this regard, what happened with the so called "Ebola case" is of great interest, the disease in itself though rare encompasses the added danger of being contagious and rapidly spreading, which can turn into an epidemic with a high mortality rate, this makes it even more urgent to attempt to find a solution, in the interests of the individual, as well as the community.[15]

In whatever way one perceives the matter of "compassionate treatment" within or outside of trials, questions arise to which it is not easy to give a definite answer.

Is it licit to prohibit a treatment in the name of "safety" when the only "certainty" the patient has is that of death, in the short term? And what about when the risk is not only personal, for an individual patient, but the health of entire communities is at stake, as in the case of contagious diseases with high mortality? Is this prohibition licit when the patient has given consent, aware of the fact that the treatment is very high risk? To what extent is the patient free to dispose of his body, when the alternative is certain death, considering that from this act no commercial profit is derived? Would it make sense to call into question the "precautionary principle", in relation to the conditions of uncertainty and risks, when any adverse events might occur when the patient is, presumably, no longer alive?

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[14] We do not go into the merits of the specific problems of advanced therapies i.e. the treatments involving the use of materials based on cells and tissues, for which the EMA applies the same safety criteria applied for pharmaceutical products. It is a complex issue that has a significant role in the case of "compassionate care", but it requires a specific analysis which may be in future the subject of a separate ICB opinion.

[15] However, the spread of the contagion may not be sufficient to allow compassionate care only in these circumstances and therefore, for these patients, become an advantage. If we consider the point of view of the person affected by a rare disease, with a high mortality rate even though not contagious, the absence of the risk of it spreading paradoxically would deprive these patients of opportunities which others have to attempt a cure.

A hypothesis to be considered is the one in which the patient consciously requests therapy which has not yet been through phase I of clinical trials, but he is not able to access it autonomously, and requires medical intervention. In this specific situation, according to the principle of autonomy, in order to invoke the right to "compassionate treatment" various scientific evidence should be found regarding the reasonable probability that the product can be beneficial, and that the risk is proportional to the possible benefits. The reasonableness should concern the minimum level required of available scientific evidence in this regard, without which the same treatment would be unreasonable and therefore unacceptable. This level should define both the type of information present in literature, as well as the quality of the scientific literature itself.

There should be available at least robust and abundant evidence of its effectiveness from experiments conducted on animals[16] and the scientific journals in question should be internationally distributed and *peer reviewed*, that is, whose articles are subject to evaluation by means of review by experts of equal expertise.

Moreover, conflicts of interest on the part of those taking responsibility for the prescription should be excluded, this should not be a single doctor, but rather a panel of experts specified by the NHS authorities, which in a short time and in any case compatibly with the situation of the patient who makes explicit request, is capable of expressing its views to this regard, on the basis of available scientific evidence (as in the case of the WHO on the Ebola epidemic). Precisely in cases like this, when it comes to rare diseases, studied by few specialists, for which assessments of possible treatment not yet undergoing trials are based on highly specialized scientific literature, it is likely that a single doctor (and even more so in the case of a general attending practitioner), will be incapable of judging the situation properly.

An illustrative example would be the use of non-validated drugs recently authorized during the abovementioned spread of the Ebola virus. The exceptional nature of the circumstances led the WHO, last August, to consider positively the use of treatments to fight Ebola, that were not validated

[16] In relevant animal models, and in particular in non-human primates, for example, specifically the statement of the WHO regarding Ebola.

on humans but successfully tested on animals; in this regard, the WHO spoke explicitly of "*compassionate use (access to an unapproved drug outside of a clinical trial)*". A panel of experts concluded unanimously that "it would be acceptable on ethical and evidential grounds to use as potential or preventive treatments unregistered therapies that have shown promising results in the laboratory and in animal models, but which have not yet been evaluated for effectiveness and safety in humans, provided that certain conditions are met. When formulating these findings, the members of the panel are aware of moving away from the well-established and historically developed system of regulation and *governance* of therapies and interventions"[17]. The document describes in detail the exceptional nature of the situation, and lists key considerations for the use of non-validated therapies, stating that «in the exceptional situation of the current Ebola outbreak, there is an ethical imperative to offer the experimental interventions available that have shown promising results in the laboratory and in relevant animal models to patients and people at high risk of developing the disease» provided that the specific conditions defined by the panel itself are met.

The ICB does not intend to go into the specific merits of the aforementioned experimentation, but rather into the methods of governance of this emergency: authoritative public institutions, recognized by the scientific community and international politics, such as the WHO, facing a situation of an exceptional nature, have identified an equally exceptional path, outside of the ones currently regulated according to criteria of transparency and appropriateness from the scientific point of view. In this sense, the ICB refers to the "Ebola case" as an example of health governance, regardless of the outcome of the specific trials underway.

When these conditions occur and anticipating future observations[18], the Committee intends to embrace the hypothesis that it is possible to authorize non-validated treatments (that are validatable) under the supervision of specifically authorized medical personnel, even beyond the limits currently envisaged by DM May 8, 2003, with all the precautions that will be subsequently mentioned. Within these particular cases we could therefore speak of the

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[17] Available from: www.who.int/csr/resources/publications/ebola

[18] See *ultra*, p. 21.

"Ebola case" as a means of access to compassionate use in analogy to the criteria and procedures designed by the WHO in this circumstance[19].

More critical is the indispensable requirement in any medical treatment of the informed consent.

How "informed" can consent to treatment be, if we do not know the scientific assumptions, methods of administration and the possible side effects? Informed consent is not only the assent to a particular therapy, neither is it an act of will, as such, binding on the doctor; it is rather the outcome of a process of engagement and learning based on information that should be as complete as possible. The particular ethical, deontological and juridical connotation of information/communication, should receive even greater attention, in delicate situations such as compassionate use. The profile of information constitutes for the patient a genuine right whereas for the doctor it serves as a duty. Consequently, it raises the obligation for the doctor to provide clear and receive comprehensive information, moreover, the utmost attention must be paid to this moment of empathy when the effectiveness of the treatment and its harmfulness is not very evident. The shared objective is to enable the patient to make an informed decision that is appropriate to the situation and his expectations of health, with a broad connotation given to the latter, remaining open both at the time of "*treatment*" and "*care*". The utmost transparency and clarity is required on the part of the doctor especially if the possible side effects and potential harmful effects of the therapy are unknown, so as to allow patients to exercise their autonomy, in a perspective of balancement of desired effects and the quality of life remaining after truly thoughtful consideration.

Faced with treatments that have not yet been sufficiently tested, informed consent, even with all the limitations due to the peculiarities of the situation, can only be in part a declaration of personal acceptance of risk, considered valid only if expressed after encountering physicians who agree on the reasonableness of the request.

The absence of validated treatments cannot, however, make consent to an alleged cure which lacks any rational justification legitimate, it being

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[19] Clearly in the above example of early access, the assessment is less problematic because of the ascertained absence of harmfulness.

founded only on the will of the patient. Otherwise there is the risk of transforming patients from victims to be rescued into guinea pigs to be exploited. It is easy to move from compassion to illusion, only to endorse practices which have no justification in our legal system and no scientific and bioethical foundation.

2. When severe fatal pathologies affect children, as is the case with many rare diseases, diagnosed in infants or babies a few months or few years old, the issue of "compassionate treatment" takes on an absolutely dramatic importance. Feelings of helplessness and the will to preserve hope against all evidence often go hand in hand, fuelling each other. One is ready to do anything faced with the innocent suffering of one's own child, and it is no coincidence that the "Stamina issue" has taken on stronger tones with regard to rare diseases in young children.

But reacting to the endless pain of these circumstances with illusive and deceptive therapies is the greatest cruelty that can be inflicted to families already so sorely tried, and it is the very opposite of "compassion".

What has been said so far about the issue in question can be extended to patients which are minors, with some clarifications regarding prescription and informed consent. The panel of experts, eventually called upon to rule on the possibility to prescribe "compassionate treatment" to minors, should necessarily include neonatologists or pediatricians with proven experience for the age group of the children involved in such treatments. Among the criteria for prescription it is essential, in fact, to take into account the huge differences in levels of development among the people within the category of "minors".

With regard to informed consent, by parents or legal guardians, as generally occurs in the context of health care, it must involve children proportionally to their age, maturity and awareness of the situation in which they find themselves.

Nevertheless the problem of how to give voice to the child is a delicate one, without adding to the trauma of illness the trauma of information which becomes more tragic the clearer and more complete it is. Appropriately in the document on *Information and Consent to Medical Acts* June 20, 1992, the Committee devoted a special section to the "informed consent in pediatrics", moving from the idea that "...the conception of informed consent in

pediatrics is different, due to the undoubted impression received from the knowledge and perception of reality in children and adolescents, their development in the environment, the way they belong to the world, the way of belonging of their parents, and the capting of their verbal and analogical communications, expectations, requests and proposals". To ask, at such a delicate moment of development, to decide on their own life can have a profound effect on their trust in the ability of "grown-ups" to provide aid and assistance[20]. We will never have the certainty that the search for the opinion of the child does not end up unwittingly and indirectly, in determining the loss of all illusion, but we will never even be sure that by doing the opposite, relegating the child to ignorance and incapacity, that we are operating in the best way to guarantee his good. The subsequent ICB document *Bioethics with childhood* 22 January 1994 states, for example, that "children with a chronic illness, duly informed about the characteristics and long-term treatment, demonstrate their capacity to accurately carry out requirements. It has been demonstrated in children with asthma that providing adequate information decreases the number of medical consultations and the frequency of hospitalization".

Therefore, we cannot ignore the will of the child, neither the existential sacrifice that is entailed by the loss of illusions and hopes. The principle of autonomy demands the recognition of the dignity of the adult, but the principle of beneficence could prompt a delay for the entry into the adult world, constrained by illness and suffering. How should a correct bio-juridical classification of the will of the minor be given? One could speak of a compulsory, but not binding opinion; or of a weak autonomy only "potentially decisive"; or a non-binding opinion *prima facie*, that becomes binding once assumed.

It is fundamental in this regard that the child and his family members are not left alone. The role of associations is of particular importance, tending to bring closer both the families taking charge of their loved ones and the young patients themselves. This associationism comes from the desire, if not the necessity, to share a painful experience, as well as the skills so la-

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[20] "Children are much more fragile than adults, less able to be resigned to the advance of illness, more frightened by biological and corporeal situations, which they often do not fully understand the origin and meaning" in P. CENDON, *Cellule staminali somministrate ai bambini sofferenti di gravi malattie neurologiche,* in "Minorigiustizia", 2013, 2, p. 241.

boriously and painfully acquired in the field. Very often it is this sharing of common experiences that is the best antidote to the spread of illusory promises of therapies that are decisive or at least "miraculous" on one hand, and on the other it is a unique opportunity for the diffusion of good practices, even "compassionate" ones.

3. In these situations the "right to hope"[21] has often been invoked. But is there such a right?

In this experience of pain and suffering the sick patient can find strength and support in the daily hope of healing or at least of not seeing his condition deteriorating. He may also have faith in the advancement of scientific research and the experimentation of new treatments which may be of benefit to his health and the health of other patients in the same conditions. In extreme cases hope may go as far as the taking of a risk, on the basis of a positive personal attitude, willing to pursue a remote possibility, on the basis of a certainty that a solution may exist, for example by following non-validated or experimented paths.

The Committee observes, faced with such a human and respectable sentiment (nevertheless it cannot be interpreted as a "right"), that the only way that institutions have to guarantee "hope" for the patient to find a therapeutic solution is the control of "how" they are treated and over "those who they place their trust in".

The compassionate use of a drug must be the exceptional situation that leaves space for a gleam of hope, but which excludes any space for speculations that are fuelled by illusions.[22] It is the same Constitutional Court (no. 185/1998) to recall, regarding special and temporary authorization for the

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[21] A Right invoked in several judgments in our country, especially in the "Stamina" Case. In the United States it is invoked as the "right to try". Significantly, in several states (Colorado, Louisiana, Missouri, Michigan, Arizona) there have been specific laws enacted regarding this "right to try", to allow quick access to the drugs being tested, without being subject to the restrictions of the US Food and Drug Administration.

[22] As emphasized by the International Society for Stem Cell Research, in the *Guidelines for the Clinical Translation of Stem Cells,* 2008, one must bear in mind the difference between the illegal marketing of interventions with stem cells not adequately tested and the legitimate attempts at medical innovation outside the formal context of clinical trials. It therefore invites the regulatory authorities of various countries to prevent exploitation of the credulity of patients, closing the clinics in which this fraudulent activity takes place and taking disciplinary action against the doctors involved.

therapeutic use of drugs outside of trials, that in cases of extreme therapeutic requirements, that are urgent and without alternative answers that the expectations comprised in the minimum content of the right to health care undoubtedly arise. At the same time it appealed to distinguish between hope in "any treatment deemed effective" and the therapeutic hope based on strict objective parameters (drugs under clinical trial and a special temporary authorization for therapeutic use), and subjective parameters (the doctor considers under his own personal responsibility, and on the basis of objective elements, that there are no valid therapeutic alternatives using already validated medicines or treatments for these diseases) and temporal parameters (at such time it is not possible to have scientifically reliable data).

It is crucial that doctors, as well as legislators and judges, in an attempt to give voice to the requests of those suffering, never lose sight of the fact that therapeutic hope must be based on reliable scientific bases.

4. On the side of the Institutions

The term "institutions" refers to all the subjects involved, in various capacities, in the process of the "government" of the administration of drugs and have the responsibility of ensuring quality and safety of clinical treatments: National Health Service, Ministry of Health, National Institute of Health, AIFA, hospital facilities, ethics committees, doctors and judges.

The administrative and juridical regime of assessment of the effectiveness of a drug or a treatment responds to requirements of social security. Requirements imposed to guarantee both the health of the citizen as well as the proper functioning of the public administration. It should also be borne in mind that the administration of drugs and therapies requires a delicate balance in the allocation of resources. With the consequence that, from the point of view of the institutions, until the administrative process governing marketing has been completed, the drug does not constitute a valid therapeutic response to the disease and therefore does not come under the right to health.

In derogation of this principle, the "compassionate use" of drugs implies a different involvement of the various levels of governance. We have a kind of reversal of the decision-making process that is no longer directed from above, from the decisions taken by the political and administrative authorities, but it moves from below, from the immediate and undeferrable in-

terest of the patient, certified by the doctor's prescription, to then go up, back then, to the other steps of the public and private institutions: from the pharmaceutical companies that must provide the drug to the hospital facilities that are called to administer it.

The judge intervenes, in turn, when a conflict between the different levels is determined. The delicate point is the existence of efficient connecting bodies, both scientific and ethical, which can ensure, in a short time and with adequate information, a proper level of interpenetration between individual choices and general interests, avoiding (as in the case of the "Stamina method" and even earlier with the case of the "Di Bella therapy") that systematic and constant recourse to the courts that has determined the end of each matter in itself, without any guarantee of respect for the principle of equality and evaluation of general interests . The constitutional principle of the division of powers and the subjection of the judge to the law imposes, even before the most dramatic situations, to operate in compliance with established scientific parameters without confusing the expectation of relief and the desperate search for a remedy with the right to health.

This dual mode of developing the decision-making process, "from the top" or the "bottom", reflects the diversity of requirements that are implicated, both fundamental in the configuration of the right to health. The first requirement regards the monitoring of the scientific reliability and the procedural rigor of the trial in order to ensure a standardized and generalized fruition of the drugs. We have a preliminary assessment of the benefit-cost ratio entrusted entirely to the regulatory authorities. The second requirement relates to the duty to not foreclose the eventuality of survival or improving the quality of life of the single person who is suffering. In this case the evaluation of the ratio between benefits and costs lies essentially with the patient and the attending doctor, with individual effects that can only be evaluated *ex post*.

These two requirements are different. One cannot be assessed exclusively with the canons of the other, neither can one even be implemented, altering the structure of the other. The task of institutions is precisely that of trying to make them as compatible as possible.

Therefore the role of ethics committees is particularly delicate and recalled by the DM December 5, 2006 in relation with the art. 6 of Decree 211/2003 on the testing of medicines for clinical use. The judgments given

on the "Stamina case", for example, configure on the role of ethics committees four different hypotheses in relation to a far from clear regulatory framework:

a) The committee's opinion is irrelevant because it can not affect the doctor-patient relationship and the patient's freedom of healthcare.

b) The opinion must be requested, but it is not binding for the doctor.

c) It is necessary and binding, but it is sufficient if it has been provided on a similar case.

d) It is necessary and binding and must be expressed case by case.

The ICB stated in the Note of 16 January 1998 regarding the cancer therapy given by Prof. Di Bella, that "if an ethics committee structure is requested to give an opinion, which does not imply an organic experimentation according to current regulations, but solely a judgment of ethicality or otherwise of an unusual or alternative therapy, practiced on a single patient, the committee's opinion is however not binding because it is up to each individual physician, the professional responsibility for decisions on innovative and alternative therapies cannot be delegated, it can be broadly favourable, provided that there is, in that particular case, on the one hand the gravity of the patient's conditions, and on the other the uselessness of other established therapies, such as to constitute a real state of necessity that can justify any reasonable attempt at a therapeutic alternative".

As can be seen, the regulatory gap, in this case, is particularly evident. A comprehensive legislation is needed which clearly defines the role of ethics committees and their relationship, when it comes to non-validated treatments for personal use and not repeated treatment, with the autonomy of medical choices.

Particularly delicate, in these cases is, the recourse to procedures for convening and emergency decisions where it is always more frequent the online regulatory provision for deliberations, these do not allow for adequate discussion and effective weighting of the plausibility of the treatment, the sufficiency of scientific information, the relationship between risks and benefits.

It also raises the issue of whether or not the patient is entitled to non-validated treatment under the NHS and reimbursement of costs. As is known, in Italy the reimbursement of the cost of medicines and medical

treatment is provided to patients under a system which divides into different classes, A (paid by the NHS), C (cost is borne by the patient) and H (attributable to the hospital), where usually the total reimbursement is approved for essential medicines with proven efficacy intended for chronic conditions. Even the Constitutional Court (no. 274/2014) in a decision on the Stamina case explained that "the promotion of a clinical trial to test the efficacy and exclude harmful side effects of a new drug does not allow as a rule, to charge in advance to public facilities the administration of the drug itself: and this is for obvious reasons of health protection, in addition to the requirement of proper use and allocation of funds and resources at the disposal of the NHS". Nevertheless, the legislator has on more than one occasion mitigated the objective rigidity of the system not excluding charging to the NHS the administering of drugs not belonging to class A when they are essential for the treatment of serious diseases in a prolonged therapy. Not yet excluded by the NHS are the medicines already authorized in other States, but not in our own country, or that are not authorized yet, but undergoing experimentation, i.e. *off label* treatments, on the condition that in all these cases there is no other valid therapeutic alternative.

This is an exception that has been admonished many times by jurisprudence regarding the abovementioned cases[23]. However, these services must respect the principles of "suitability" of the drug or therapy within the parameters laid down by law, and effectiveness which requires "necessarily a comparison of the positive outcomes of health care and the possible negative repercussions of the therapy on the living conditions of the patient"[24].

In concerns to "compassionate" treatments and drugs there is no clear regulatory framework that ensures, on the one hand, to the doctor, in the sphere of his discretion, the legitimacy to prescribe a non-validated treatment (although judged appropriate according to best knowledge and belief) and, on the other hand, the adhesion of the State with the consequent acceptance of its financial costs.

A hypothesis that the committee endorses is the one indicated above as "the Ebola case." The NHS may allow the patient, even beyond the limits

[23] See among others, Cass. no. 1665/2000; Cass. no. 2034/2000; Cass. no. 18676/2014.
[24] Cass. no. 18676/2014.

currently envisaged by Ministerial Decree 8 May 2003, to receive non-validated treatment, under the supervision of specifically authorized medical personnel, in exceptional cases and under strict conditions: the absence of alternative therapy; urgency and emergency that place the patient in danger of death or rapidly progressive serious disease; authorization and monitoring entrusted to a panel of experts or institutional committee; real-time publication of all the results.

In the case of a patient admitted to an accredited public or private facility the drugs should be charged to the NHS seeing as the costs on admission are inclusive of the pharmaceutical treatment carried out (see, ex. p.32 Legal appendix: e.g. L. 94/1998); however in these cases given the high cost, it would be appropriate if this was borne by the manufacturer of the drug, who receives, in any case, a benefit from the information that is acquired.

A delicate aspect arises when the recruitment of single patients involved in compassionate use, interferes with the protocols of the actual trials: in this case, in the ICB's opinion, the anecdotal outcomes must be presented separately from the final results of the clinical trials authorised in compliance with standard procedure.

In order to avoid creating easy illusions, to prevent running into speculation and to strengthen the support network and support to patients and family members, the ICB considers it to be a bioethical duty of public health institutions to encourage the spread of clear scientific information on accredited sites by authoritative bodies or research institutions[25].

5. On the side of the doctor

We refer in this section to "doctor" in the singular, giving this word also the meaning of "panel of experts" in the terms illustrated above. As can be seen from what has been observed previously, the doctor performs the most delicate role, because he is as much the representative of the institutions and the guarantor of the proper application of treatment protocols as the participant to whom the suffering and despair of the patient and his family, he experiences, often almost with a sense of guilt, the full weight of helplessness,

[25] Recommendation already present in ICB, *Ethics, Health and New Information Technologies*, April 21, 2006.

of not being able to provide adequate relief. The dramatic situation may result in mutual pressure, between patient and doctor: one expects a remedy at any cost and the other tends to provide it in every way. Torn between resignation that is difficult to accept and compassion which is difficult to achieve, the doctor has the duty to advise the best treatment "available", but in the absence of known remedies the concept of "availability" becomes vague, extending to the probable and possible. Does it even extend to what is supposed? What is the threshold beyond which it is not permissible to go?

The response should be found in the difficult relationship between the maximum benefit hoped for and the least harm foreseeable. In this weighting a part of jurisprudence holds that even a "mild" improvement or even only the hope of an improvement could have its own weight. From the logical point of view the opposite argument is just as plausible: if we are not sure that a drug "does some good," neither can we say that it does no "harm"; if the benefit is not predictable, neither is the foreseeable damage.

It is not possible to expect to circumscribe in a clean way the margin of appreciation left to the doctor in the assessment of these critical situations.

If the doctor cannot become a seller of illusions or a hired conscience endorsing any request, neither can he ignore, in the primary interest of the health of the patient, the innovative therapeutic prospects that seem plausible to his professional conscience.

Therefore, differences can emerge both in the assessment of the performance of individual doctors as well as in the relationship between the doctor who prescribes the treatment and the doctor who is called upon to implement it. The ICB notes that, in this case, the doctor called upon to administer a therapy, prescribed by others, for "compassionate" reasons, has not only the right but also the duty not to carry it out, if he does not believe in its effectiveness or if he believes that it may be absolutely dangerous. The right to professional autonomy and the duty to respect, according to best knowledge and belief, the dictates of *lex artis* prevail over the possible need to ensure therapeutic continuity. This is not a case of conscientious objection, because we are not dealing with a conflict of values or different visions of life, but the respect of those fundamental principles that form the basis of the medical profession.

Although an unfathomable margin left to personal evaluation cannot be eliminated, regulations that provide clear guidance to the doctor are essential, as part of a weighted evaluation of the relationship between the social profiles

of the right to health care and the subjective margins of freedom of treatment, a valid support in the taking of responsibility. The recent events in Italy highlight how difficult it is, within a plurality of heterogeneous regulations enacted at different times and for different purposes, to have a correct assessment of the many possible situations within the recourse to innovative practices for "compassionate purposes". All this makes even more difficult and dramatic the condition in which the doctor operates and promotes the emergence of speculative phenomena that exploit desperation and fuel easy illusions. Faced with such delicate situations, the ICB believes there must be provision for methods of judgment that reflect the complexity of the cases treated, by requiring that the therapeutic treatment does not come only from the attending physician, but it should receive the support of qualified specialists in the form of expressed authorization by a specifically dedicated panel, appointed by NHS institutions, and submitted to the approval of the ethics committee, under whose area of expertise the request pertains[26].

In addition, the profession of a doctor is not limited to the administration of treatment. He has to monitor the progress of therapy, making appropriate assessments about the effects that the therapy has on patients from time to time. It also follows that the doctor must ensure the requirements of the traceability of the product and the patient treated and reported to the bodies deputed for this by the State for the clinical data on adverse events and the outcome of treatments carried out.

6. Conclusions

The dramatic nature of serious diseases for which there are no effective and validated treatments sometimes places those involved - patients, institutions, doctors - in tense situations if not, sometimes, in mutual opposition to the rights, duties, hopes and expectations of each. In the light of the reflections and considerations, the ICB believes that these situations can be addressed more adequately in accordance with the following guidelines:

1. It would be advisable to use a different term for "compassionate

[26] For our country see art. 4, par. 2, letter a) of Ministerial Decree entitled *Therapeutic use of investigational medicinal product* of 8th May 2003.

care", so as not to confuse it with legitimate feelings of empathy for patients with serious pathologies resulting in fatal outcome, very often children. The ICB in this regard suggests: "non-validated treatments for personal and non-repetitive use" and calls for a "*consensus conference*" in order to adopt appropriate terminology that is shared internationally.

2. Such treatments are allowed in exceptional cases, when there is no validated therapeutic alternative in cases of urgency and emergency that put the patients in mortal danger or serious rapidly progressive pathologies; they cannot be an explicit or surreptitious alternative to clinical trials, nor can they mean to replace it in any way.

3. The administration of these treatments must refer to a specific indication and normally based on multiple reasonable scientific evidence, namely: data published in specialized magazines with international circulation and *peer review* evaluation which include at least robust and evident results regarding animal testing for efficacy and toxicity and possibly with Phase I results on human beings.

4. This therapeutic prescription can not only come from the treating physician but must receive the approval of the Ethics Committee in whose area of expertise the request pertains. In addition, is necessary the support of qualified specialists for the diseases for which compassionate treatment is requested, preferably in the form of expressed authorization by the specific panel, designated by public health institutions called on to express an opinion in a short time. In the event that the patients concerned are minors these panels must provide for the presence of neonatologists or pediatricians with proven experience in the age group concerned.

5. It is necessary to avoid both conflicts of interest for those who are prescribing or administering or authorizing the treatment, as well as elements relating to possible speculation of an economic and industrial nature.

6. The composition of the products used for the treatments must not be secret, be they synthetic or biological in origin. All results both positive and negative must be made public.

7. Since it is a request for non-validated treatment, it obviously cannot be binding on the physician.

8. For patients who want to have access to a "compassionate" therapy there must be the guarantee of receiving complete explanations on the potential dangers of this type of treatment.

9. The cost of the non-validated drugs normally must be borne by the manufacturer, while the relative monitoring must be headed by the specific facilities and public health institutions.

10. When the above mentioned points are met, "compassionate" treatments can be considered ethically licit and come under the general right to health.

A Personal Remark

Remark signed by Prof. Salvatore Amato and Prof. Assuntina Morresi

Hope is a risk worth taking (G. Bernanos)

The coordinators of a working group are responsible for examining in depth the issues related to the subject matter to be reflected on by the ICB, to collect all the positions, to prepare a written text that will form the basis of the future document and...to step aside. To step aside if the majority decides to develop arguments, or even conclusions, other than those which they had initially hypothesized. In this sense, the opinion does not belong to the coordinators more than it belongs to every member of the Committee who, by voting it, has approved the contents. The reason for this short note is not in disagreement with a text that we agreed upon with the great majority of my colleagues, but rather in the fact that two aspects of the problem of "compassionate treatment" have not seen an accentuation or declination which to us seemed essential. Ours is, therefore, a sort of "*concurring opinion*", for further adhesion to the document, reinforced by a few other considerations.

The first aspect and the most important, concerns the issue of freedom of treatment. The right to health has many facets, but it is undeniable that the freedom of treatment constitutes the central nucleus. Long quotations are not appropriate in an ICB document, but we believe they can find room in a "note", just to give an overview as complete as possible of the current debate.

Here for instance is what Amedeo Santosuosso writes: "Freedom of care is a fundamental right of every individual whether it is understood as an absence of the obligation to accept medical care, using any method effective or ineffective official or alternative. The ultimate expression of this freedom is the total refusal of health care, letting the disease take its course: this is the basis of every freedom and every right. The freedom to choose the method of health care is grafted onto this fundamental freedom"[27].

It therefore appeared necessary to us to identify the problem of compassionate use of drugs surrounding the ICB opinion of *Refusal and conscious renunciation of health treatments in the patient-doctor relationship.* We did not want to claim that the " Stamina case" was a consequence of the right to refuse treatment but rather to reflect on the right that the individual has on his own body and if this right does not also include even a tragic and painful right to "self-experimentation". Some American states have recognized in extreme situations the existence of a *right to try* to be enforced even against pharmaceutical companies who denied the utilization of a drug not yet validated by the FDA.

So we take this opportunity to reiterate some of the concepts that unlike the majority of colleagues, we deem it necessary to describe more thoroughly the issue in question.

Although the aforementioned opinion *Refusal and conscious renunciation of health treatments in the patient-doctor relationship* does not explicitly touch the problem of so-called compassionate treatment, however, it poses a number of important conditions that affect the evaluation of the patient's right to undergo non-validated treatment in the absence of an alternative. This document outlined several key points: the rule of informed consent "allowing the full valorisation of the choices made by the compe-

[27] A. SANTOSUOSSO, *Un altro caso Di Bella?*, in "Minorigiustizia", 2013, 2, p. 250.

tent patient based on the principle of autonomy"; the right "to maintain control over what happens to one's body and one's life"; "the right to obtain otherwise the realization of one's request for the termination of health care, even in consideration of an eventual or possible abstention by the doctor or medical team".

Here then we reiterate the question that in our view was partially circumvented: this right to decide what is good for oneself, in setting the parameters of one's "own" health, does it also entail a kind of right to self-experimentation, obtaining, without burdening the NHS service and with the endorsement of a prescription the administration of innovative therapies or even therapies without any adequate scientific evidence?

We are aware of the substantial difference that exists between the right to refuse healthcare treatments, which is based on "nothing on my body without my consent," meaning the "protection of the psychophysical freedom of a person whose bodily dimension must be respected" and instead the right to obtain, especially if not validated, a difference also emphasized in the opinion on "compassionate care".

Setting aside this issue - that of having to draw the boundaries of freedom of health care and the autonomy of informed patients - one may be faced with the following paradox, reiterated by some patients who have strongly requested access to compassionate treatments: a person suffering from a serious fatal disease that consciously decides to die, suspending life-saving treatment or artificial nutrition and hydration, would be entitled to do so, in the name of his own competence, autonomy and awareness, so as to demand the implementation of his wishes even if the doctor was opposed to this, by searching for other doctors. If the same person wanted to try to even just improve the quality of life, with the certainty of impending death, consciously taking responsibility for the risk of a non-validated treatment, his consent, competence, autonomy and awareness, along with the conviction of a doctor, would no longer have validity in the name of "safety" for his health, established by a regulatory authority.

We believe that so-called compassionate treatments are ethically permissible only within the strict framework identified in the opinion that we approved.

At the same time, however, we cannot but think about the consequences that go with the freedom of treatment and patient autonomy, which

inevitably result therefrom reconsidered within a perimeter determined by the appropriateness of treatments (defined according to objective and criteria) and the autonomy of the experts who reserve the final decision in this regard.

The second aspect that we believe we should integrate is the "right to hope," that we dealt with in the opinion because we were directly called upon to act by a number of judgments in the "Stamina case", as well as in the literature in English. We do not believe that the plethora of rights that obsessively crowd legal texts and very debatable rulings should also include that of hope. But we think that in a paragraph entitled "on the side of the patient," the motivations of those who claim to have this right should be further discussed, to avoid falling into "bioethical paternalism" to the detriment of the completeness of representation of all the factors at play.

This is why we deem it important to emphasize that this request comes from the fact that there is no doubt that patients are waiting and are hoping for treatments. Hope is an existential attitude that includes in itself the wait, literally "expecting", it appears mostly as a "waiting" trustful in the help of science and medicine respecting the schedule and rules of scientific research. But hope, even in the motivation, may lead to taking personal risk by virtue of a positive personal attitude, a desire to pursue a glimpsed opportunity, in the conviction that a solution may exist, for example, along not validated or experimented paths.

The "right to hope", in this perspective, therefore means the personal right to taking a risk in view of a possible positive solution (where the category of "possible", is different from that of "probable" in a statistical sense: "possible" means that it can happen even just once, even if it has never happened before, and it is not reasonable to exclude it occurring, while "probable" indicates a measured and quantified certainty based on events that have happened or however are foreseeable according to models).

Even in this case we resort to a long quotation to emphasize how this view is widely held in literature and in doctrine, therefore the Committee should have considered it in quite a different manner.

On the reasons that justify compassionate treatments, Cendon writes: "[...] they appear dictated (to recall the vocabulary used by the Italian and European legislator, by judges, and doctrine, in these matters) by consideration on pietas, solidarity, humility, benevolent spirit, lack of alternatives,

conjectural availability, mercy, therapeutic realism, comparative pragmatism, human understanding, in relation to individual cases"[28].

We believe that the expression "right to hope" arises from this position, and not from a feeling albeit respectable but - implicit - that is totally irrational and unfounded; and it is this position entirely that has to be dealt with and responded to, without censorship. For this reason we agree with the appropriate definition of hope given by G. Bernanos "hope is a risk worth taking", in the framework of reasonableness identified by the approved opinion, outside of which it would not be a question of hope, but of cruel illusion.

[28] P. CENDON, *op. cit.*, p. 236.

ATTACHMENT:

A JURIDICAL NOTE

1. In Italy, the legal framework is based on art. 32 of the Constitution that guarantees health as a "fundamental right of the individual and collective interest". This right, however, is divided into a plurality of positions, characterized by content and intensity of the different protection.

The administering of new drugs and their marketing are a key aspect of this right. They are, therefore, subject to statutory regulation imposing the requirement of a preliminary ministerial authorization. The treatments and cures that fall within this category and that are regularly provided have passed through all the stages of testing and have obtained approval by the scientific community regarding their innocuousness and effectiveness. In the context of validated drugs those which fall within the category LEA category (Essential Levels of Care) should be guaranteed throughout the national territory in conditions of equality for all persons (citizens and non-citizens) and be free of charge or shared charge, after that is, payment of the prescription charge (Law 537/1993).

Therefore, the present case of so-called compassionate treatment is outside the therapeutic practices generally regulated. There are, however, exceptions to the ordinary institutional forms of administration of drugs or other therapeutic treatments tested.

Firstly to be mentioned, although dated, is the Legislative Decree 178/1991, which aimed at establishing the areas of legislation *de qua*, and provided for certain exemptive situations: in par.7, letter b) it gives the doctor the option to request the national or foreign production of medicines to be administered at his own responsibility to the patient prior to regulatory approval and for a period not exceeding thirty days. The rule is still vague since it does not make explicit the conditions for which the doctor is authorized to request treatment outside the rules, thereby marking a strong discretionary power of the doctor in assessing the most appropriate treatment for the patient, including also compassionate treatment.

More detailed regulation regarding compassionate treatment and reimbursement by the NHS is deductible by Law no. 648, 23 December 1996 (the result of conversion of Decree Law no. 536/1996). Under art. 1, par. 4

of the law, where there is no valid therapeutic alternative it may be dispensed fully charged to the National Health System: a) innovative medicines on the market in other States, but not in Italy; b) medicinal products not yet authorized, but actually undergoing clinical trials; c) medicines to be used for a therapeutic indication different from the one approved; all included in a special list drawn up and regularly updated by the Committee on the Safety of Medicines in accordance with the procedures and criteria adopted by the same committee.

In this regard, however, the limited scope of the provisions has been clarified. The Committee on the Safety of Medicines has noted that "falling outside the scope of the quoted norm is the treatment restricted to individual patients, following an assessment of their specific medical conditions, with registered medicinal products for other therapeutic indications. In such circumstances, assignable to the situation governed by art. 3, par.2 of the Decree-Law 17 February 1998, no. 23 converted with amendments, into Law 8 April 1998, no. 94, charges are borne by the patient in accordance with par. 4 of that article. It is understood that the use of the medicine for the benefit of a patient admitted to a public or private accredited facility is borne by the National Health Service, since the hospitalization fee is inclusive of the cost of the administered pharmacological treatment"[29].

Of relevance is also the regulation of the use of *off-label* drugs, the provisions of which, in addition to in the Law 1996 no. 648, are chiefly contained in the Law April 8, 1998, no. 94 (Conversion Law Decree 17 February 1998 no. 23).

For the use of *off-label* drugs it is meant, for the purposes of the aforementioned legislation, the use of drugs: a) for therapeutic indications other than those contained in the marketing authorization; b) given in different doses to those contained in the instruction form of the medicine; c) to persons included in different age groups instead of those to which are commonly prescribed.

If in general, the doctor, when prescribing a medicinal product, must follow the therapeutic indications and the mode of administration provided

[29] This is press release 04.07.2002 on the scope of art. 1, paragraph 4 of Decree Law October 21, 1996, no. 536, converted by Law of December 23, 1996, no. 6.

by the marketing authorization issued by the Ministry of Health, the 1998 Law no. 94 provides a number of exceptions to this principle, giving to the doctor a degree of autonomy, accompanied by a corresponding individual responsibility. In exercising that autonomy, the professional must always refer to a set of criteria relating to the accuracy and adequacy of his professional work. In particular, the doctor can legally prescribe an *off-label* drug only in the presence of three competing requirements: 1) inability to effectively treat the patient *in-label*; 2) obtaining the informed consent of the patient; 3) compliance with the *off-label* drug use in relation to articles that have appeared in accredited scientific publications, even at the international level[30].

In this regard, it should be remembered that the Code of Medical Ethics, in its latest version (2014), indicates partially equivalent conditions: the doctor may prescribe medications for indications or dosages not covered by the data sheet, if their safety and efficacy is supported by science and the risks are proportionate to the expected benefits; in such cases it justifies activity, acquiring the written informed consent of the patient and assessment of the effects in time[31].

The "compassionate use" is reflected in Ministerial Decree May 8, 2003, named "Therapeutic use of drugs undergoing clinical trials." It provides for the possibility of use of a medicinal product in the pharmaceutical facility authorized or regularly imported, which is undergoing clinical trials in Italy or abroad, for the use outside of experimentation, in the case where there is no valid therapeutic alternative to the treatment of serious pathologies, or rare diseases or life threatening disease conditions. Under art. 2 of

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[30] Art. 3 par. 2 of Law no. 94/1998 states that "the doctor may, under his direct responsibility, and after informing the patient and obtaining the consent of the same, use a medicine manufactured commercially for an indication or means of administration or a method of administration or use different from the one authorized or recognized to the effects of art. 1, par. 4 of Decree October 21, 1996 n. 536, converted into Law December 23, 1996 n. 648, if the doctor thinks, based on documented data, that the patient cannot be successfully treated with medicines already approved for that therapeutic indication or that means or method of administration and provided that such use is known and is in conformity with articles that have appeared in scientific publications accredited internationally".

[31] The seventh paragraph of art. 1 of the Council of Ministers 2014 states: "The doctor can prescribe drugs not registered or authorized for trade or for indications or dosages not covered by the data sheet, if their safety and efficacy is supported by science and the risks are proportionate to the expected benefits; in such cases it justifies activity, acquiring the written informed consent of the patient and assessment of the effects in time".

the law two conditions must still be complied with: a) that the product is already the subject, in the same specific therapeutic indication, of experimental clinical trials, ongoing or concluded, either in the third phase or, in the particular cases of life threatening diseases, in clinical studies already completed or in the second phase; b) that the available data of the trials referred to in a) are sufficient to formulate a favourable opinion on the efficacy and tolerability of the drug.

When these requirements are met it is also envisaged that the pharmaceutical manufacturer provides the supplying of the drug free of charge (par. 3 of art. 4 of the Ministerial Decree). The medicine can then be requested: a) by the doctor for nominal use on a single patient not treated in clinical studies (individual compassionate use); b) by multiple doctors; c) by doctors or collaborative groups for patients who have participated in a clinical trial demonstrating an efficacy and tolerability such as to represent a need, for the same patients, to benefit at the best possible time from its findings (group compassionate use).

The manufacturing company may provide the medicine on the basis of a protocol in which are reported among other things the clinical grounds for the request, the data on efficacy and tolerability, the procedures for informing and patient consent. The protocol should also be submitted by the doctor (who however bears the responsibility) to the approval of the relevant ethics committee which can also operate by urgent procedure and forwarded to the Office for Research and Clinical Trials of the Italian Pharmaceutical Agency that, where appropriate, may issue an opinion of suspension on the procedure or use.

The supply of the material by the producer is subject to the favourable opinion of the ethics committee.

A form of accountability due to violation of the Protocol is provided for in art. 22 of Decree Law 211/2003 implementing Directive 2001/20 / EC which, however, merely provides for administrative liability of a pecuniary nature.

Considering specifically advanced therapy medicinal products reference must be made to the decree "Turco-Fazio" (Ministerial Decree 5 December 2006): "Use of drugs for gene therapy and somatic cell therapy outside of clinical trials and transitional norms for production of such medicinal products", followed by the decrees for extension of 18 December 2007 and 24 December 2008.

Under this regulation medicinal products for gene therapy and somatic cell therapy can be used on individual patients subject to certain conditions, given by the lack of valid alternative therapies, in case of urgency and emergency in which the patient's life is in danger or damage to health and in the case of serious rapidly progressing diseases (art. 1 co. 4). Also in this case the doctor prescribes this treatment under his own direct responsibility while, as regards to the quality of the medicine, the responsibility is borne by the director of the production plant laboratory. The prescription of these drugs and therapies can take place only when: 1) there is available scientific data to justify its use (published in accredited international journals); 2) the informed consent of the patient has been acquired; 3) the favourable opinion of the ethics committee concerning the relationship between the hypothesised benefits and foreseeable risks in relation to the patient's condition has been acquired; 4) in the case where the medicine has been produced by laboratories in possession of the requirements contained in art. 2 and however in compliance the pharmaceutical quality requirements approved by the competent authorities, while, if the drug has not been tested in Italy, there must be ensured respect for the requirements of pharmaceutical quality approved by the Institute of Health; 5) treatment should be carried out in institutions of in-patient care of a scientific nature, or equivalent public facility.

Since 2009, D.L. no. 219/2006 has entered into force (implementing Directive 2001/83/EC and 2003/04/EC) regulating advanced therapy medicinal products used in individual patients. Art. 3 par. 1, f-bis[32] states that such therapy should be prepared in a non-industrial scale and that it must be administered in a hospital, only for a particular patient and under the responsibility of a doctor. This *custom made* regime, called *"hospital exemption*" in art. 28 of EC Regulation no. 1394/2007, represents even in Italy a derogation from the requirement of actual marketing of the product. In addition, treatment is outside the scope of a clinical trial according to D.L. no. 211/2003.

[32] Lett. F-bis introduced in Legislative Decree no. 219/2006 by the paragraph 1 of art. 34 of Law 88/2009 (Community Law). Further modified with the Decree Law March 4, 2014, no. 42 (Implementation of art. 1, paragraphs 1, 5 and 12 of Directive 2012/26/EU amending Directive 2001/83/EC as regards pharmacovigilance).

Italy has implemented what is indicated by the aforementioned EC Regulation no. 1394/2007 without further specifications, if not specifying that the preparation of the products under the regime of *hospital exemption* must be authorized by AIFA.

Initially, the criteria for the authorization of the law for their use were subsequently established with the decree signed on 16 January 2015 (which will be described later).

The Decree Law March 25, 2013, no. 24 ("Provisions on health"), converted into Law 23 May 2013, no. 57[33], has made possible, even after some favourable rulings in this sense, the Stamina treatment, intended as compassionate treatment, only in cases in which the treatment had already begun (art. 2).

A provision that has raised the question of unconstitutionality, with reference to arts. 2, 3 and 32 of the Constitution on inviolable rights , the right to healthcare and the equal dignity of all citizens, from the Ordinary Court of Taranto, part of the lawsuit filed by a patient who asked to be allowed to be subjected to treatment for the first time. The Constitutional Court, with judgment 274/2014 of December 5, 2014, declared that the question of constitutional legitimacy of art. 2 was unfounded. According to the Court, "decisions on the merits of therapeutic choices, according to their appropriateness, could not arise from assessments of pure policy discretion by the legislator, but should provide for the elaboration of guidelines based on verification of the state of scientific knowledge and acquired experimental evidence , through institutions and organizations - typically national and supra-national - delegated to this, given the vital importance that to these purposes technical and scientific bodies play".

Moreover, according to the Court, the promotion of a clinical trial of a new drug does not allow as a rule, to charge in advance to public facilities the administration of the drug itself: for obvious reasons of health protection, as well as requirements for proper use and destination of the funds and resources available to the NHS.

However, the Court noted that in the present case, the legislature of

[33] Conversion into law, with amendments, Decree-Law of 25 March 2013, no. 24 , concerning urgent provisions on health matters.

2013, in giving course to a trial on the use of advanced therapy medicinal products based on mesenchymal stem cells, although it has partially waived the principles set out above , it did so intervening in the particular factual situation that saw, concretely, that treatment had already begun with stem cells at the initiative of several judges who, as a precautionary measure, had ordered it to be carried out in public facilities.

An effect of the most recent Decree Law no. 36 of 2014 (converted into Law no. 79 of 2014) has been a change to the Law no. 648 of 1996 with the addition in Ch. II (Use of less expensive medicines by the National Health Service) art. 3-bis, par. 1.4 that allows the dispensing of medicines to be used for a therapeutic indication other than that authorized by the SSN, even if there is another therapeutic alternative in the context of authorized products. Even in this case, with the approval of AIFA, these medicines must be entered in a proper register, and they may be used provided their use is known and conform to research conducted as part of the medical and scientific community nationally and internationally, within the parameters of affordability and appropriateness.

On 16 January 2015 was signed the Ministerial Decree on "*Provisions relating to advanced therapy medicinal products prepared on a non-repetitive basis*" limited to advanced therapy medicinal products prepared on a non-repetitive basis. The Decree provides inter alia that: the production and use is authorized by AIFA; that producers comply with the rules on quality and safety , and traceability of the product and the patient treated and pharmacovigilance; use can only take place in a public hospital, teaching hospital or institution of in-patient care of a scientific nature, of individual patients, in the absence of a valid therapeutic alternative, in cases of urgency and emergency when the patient is in a life threatening situation or serious damage to health; use takes place under the professional responsibility of the doctor made pursuant to an individual medical prescription for a custom-made product for an individual patient, after informed consent and approval of the Ethics Committee; the results must be assessed by the Institute of Health and AIFA. The decree states that the AIFA should evaluate the application for authorization of production within 60 days and the application for authorization of use within 30 days.

2. Also with regards to the compassionate use of medicines, the important role played by the Code of Medical Ethics (2014) must be remembered. In general terms, the text defines, on the doctor part, the duties related to the protection of life and physical and mental health, to pain treatment and alleviation of suffering, while respecting the freedom and dignity of the person and without any discrimination (art. 3). The cardinal principle of the therapeutic relationship, which has a key role, is informed consent that can form a real alliance between doctor and patient; it is the condition for the full valorisation of self-determination and freedom of the person in relation to the choices concerning health. The prescription of a therapeutic treatment or medication is the exclusive competence of the doctor, who intervenes under his direct responsibility following a circumstantial diagnosis.

Although in relation to the specific case, it must take into account the scientific evidence available, subject to the guidelines accredited by authoritative and independent sources.

The doctor must therefore base his activities on the principles of clinical efficacy, safety and appropriateness, monitoring the effectiveness of the treatment on the individual patient.

On this basis, the latest version of the code of medical ethics includes some provisions that may have a specific application in terms of compassionate treatment. The last paragraphs of art. 13, sets out, first and foremost that the doctor "can prescribe medication not yet registered or authorized for sale if their tolerability and efficacy is supported by science and the risks are proportionate to the expected benefits; in such cases it motivates his actions, the acquiring of the written informed consent of the patient and the evaluation of the effects in time". Under his direct responsibility, moreover, the doctor may prescribe "drugs that have passed only the phases of experimentation related to safety and tolerability, in strict compliance with the legal system". Still, it should be noted that the professional "does not agree to the request for the prescription by his patient solely in order to please him", and does not adopt or spread "diagnostic or therapeutic practices for which there is no appropriate scientific and clinical documentation available that is assessable by the professional community and the competent Authority". Along the same lines, the doctor "should not adopt or spread secret therapies." In reference to unconventional treatment, as applicable within the context of compassionate treatment, art. 15 of the same Code adds that

the doctor "should not withdraw his patient from treatments which are scientifically based and of proven efficacy."

The action which remains within the framework just outlined is therefore licit, and falls within the sphere of autonomy and responsibility recognized to the doctor as part of his professional expertise.

3. With regard to the so-called compassionate use of medicinal products in the international context, the Declaration of Helsinki should be considered, which, although not strictly legal nor binding (having been adopted by the World Medical Association), has over the years come to be a model of reference for the entire medical profession. Art. 37 of the Declaration allows to carry on an intervention not yet tried, under the responsibility of the doctor and with the informed consent of the patient , when there are no other known treatments or interventions that have proven to be ineffective and after having sought the opinion of experts[34].

In the European context regarding compassionate use for individual patients who have not participated in the clinical trial of the medicinal product in question (individual compassionate use), Directive 2001/83 / EC (the European Parliament and of the Council of 6 November 2001 Community code relating to medicinal products for human use, and implemented in Italy by Legislative Decree no. 219/2006) provides in art. 5 that an EU Member State, in accordance with its law and to fulfil special needs, may provide medicinal products not yet on the market in response to *a bona fide unsolicited order*. These medicines must be formulated in accordance with the specifications of an authorized health care professional and for use by his individual patients under his direct personal responsibility. Also in this, in addition to the personal assumption of responsibility of the individual professional, the referral to state legislation implies the necessary presence of scientific literature related to the efficacy and the exclusion of toxicity of the product.

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[34] Art. 37, regarding interventions unproven in clinical practice: "In the treatment of an individual patient, when there are no proven treatments or other interventions known have not proven effective, having sought the opinion of experts, a doctor with the consent of the patient or his legal representative, may use an unproven intervention if according to his judgment that the drug may be a hope to save life, restore the physical integrity or alleviate the suffering of the patient. This intervention should subsequently be made as the object of study, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and made publicly available when appropriate".

The expression "compassionate use" can be traced in art. 83 of EC Regulation no. 726/2004 , that authorizes individual states to derogate from the Community rules for the marketing of drugs in the event that a group of patients with a chronic, seriously debilitating or life-threatening illness, cannot be treated satisfactorily with an authorized medicinal product.

The objectives of art. 83 are:

- to facilitate and promote access to compassionate use for patients in the European Union;

- to promote a common approach regarding the conditions of use, the conditions for distribution and the patients targeted compassionate use;

- to increase transparency between Member States regarding the availability of treatments.

Among the conditions laid down[35], in addition to the exclusive reference to the "group of patients who have already participated in the clinical trial of the medicinal product" (group compassionate use), the requirement that the medicinal product must be subject to an application for authorization to placing on the market or in any case be subjected to clinical trial[36].

Reported EC Regulation no. 726/2004 was amended by Regulation no. 1394/2007. The latter introduces for the first time the definition of "advanced therapies", including not only gene therapy and somatic cell therapy, as well as tissue engineered products. The main innovations introduced by the Regulation include: the establishment of an expert committee (Committee for Advanced Therapies), within the European Medicines Agency

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[35] The conditions are further detailed in the document "Guidelines on compassionate use of medicinal products, Pursuant to art. 83 of Regulation (EC)" no. 726/2004. Doc. Ref. EMEA / 27170/2006 "European Agency for the Evaluation of Medicinal Products (EMEA), now called the European Medicines Agency (EMA).

[36] Art. 83 of the Regulation prescribes that: "1. Derogation from Article 6 of Directive 2001/83 / EC, Member States may make available for compassionate use, a medicinal product for human use belonging to the categories defined in Article 3, paragraphs 1 and 2 of this Regulation. 2. For the purposes of this Article, for compassionate use we shall mean the making available, for humanitarian reasons, a medicine belonging to the categories defined in Article 3, paragraphs 1 and 2, to a group of patients with a chronic or seriously disabling illness or whose disease is considered potentially lethal, and that cannot be treated satisfactorily with an authorized medicinal product. The medicinal product concerned must be the subject of an application for marketing authorization under Article 6 of this Regulation or must be undergoing clinical trials. 3. Where a Member State makes use of the possibility provided for in paragraph 1 it shall notify the Agency (European Agency for the Evaluation of Medicinal Products)".

(EMA); the adoption of new requirements for quality, safety and traceability of the donation, procurement and control; the adoption of new regulatory procedures for classification and certification; support for small and medium businesses with incentives to promote entrepreneurship.

In addition, Regulation stipulates that each Member State should standardize the production and use of advanced therapies for individual patients, treated in national public facilities, and therefore not aimed at placing on the market and commercialization.

Presidenza del Consiglio dei Ministri



MEDICAL RESTRAINTS: BIOETHICAL ISSUES

23 April 2015

Presentation

The opinion *Medical restraints: bioethical issues* addresses the issue of the use of medical restraints for psychiatric patients and the elderly, highlighting the forms of mechanical restraint, which raise major concern from an ethical and juridical point of view.

Numerous standpoints of international bodies and the ICB itself in previous opinions – see: Psychiatry and mental health: bioethical guidelines (2000), Bioethics and the rights of the elderly (2006), Dementia and Alzheimer disease: ethical issues (2014) – have clearly set out the objective of the reduction to the actual overcoming of *medical restraint*, which has to be considered a remnant of the asylum culture. Nevertheless, the practice of strapping down patients against their will is still carried out, and in no way as an exceptional measure, with insufficient attention being paid to the gravity of the problem both by public opinion and the institutions.

Despite the lack of studies on this question, a certain amount of data appear available from the research regarding the variables mostly having a bearing on the recourse to the use of medical restraint: culture, the organisation of services and approach of the mental health professionals have a decisive role in this, more than the seriousness of the patients and their psychopathological profile. This demonstrates that it is possible to avoid restraining patients; the existence of services that have chosen not to apply medical restraints and the success of programmes aimed at monitoring and reducing this practice are the confirmation of this information.

For these reasons the ICB stresses the bioethical standpoint of the overcoming of the practice of restraint, within the context of a new paradigm of care based on the recognition of the person as such, in their full rights (even before being a patient). The respect for the autonomy and dignity of the person is also the prerequisite for an effective therapeutic intervention. Conversely, the use of force and medical restraint represent in themselves a violation of the fundamental rights of the person.

The fact that in absolutely exceptional circumstances the mental health professionals can resort to justifications for applying medical restraint does not take away the force of the rule of non-restraint, nor does it modify the foundations of the ethical discourse.

At the juridical level, since the fundamental rights of the person are at

stake, it is important to stress the strict limits of the justification for medical restraint. Recourse to mechanical restraint techniques must represent the last resort and it must be considered that – even in the context of the Compulsory Medical Treatment – it can take place only in situations of real necessity and urgency, proportionally to the actual needs, with the least invasive modalities and only for the amount of time needed to overcome the conditions leading to their application. In other words, the fact that the patient is in a mere state of agitation cannot be considered a sufficient condition for medical restraint to be justified, but a *serious and real* danger must exist in which the patient carries out self-harming acts or commits an offence against third parties. When such danger no longer exists, the use of restraints must cease, as it would not be justified by necessity and would amount to potential criminal conduct.

This opinion sets out to highlight that the overcoming of restraint is a fundamental element in the advance of a care culture - in psychiatric services and in the care for the elderly – in line with the ethical criteria which are generally recognised and applied in all healthcare sectors.

In its conclusions the ICB furthermore recommends an increase in research and the setting up of specific monitoring, at the regional as well as national level, starting from the daily practice in the wards where the cases of restraint should be precisely recorded, with the specific reasons for choosing to restrain the patient and the duration of the measure; *the introduction of programmes aimed at the overcoming of restraint; to introduce quality standards in the evaluation of services* that encourage *non-restraint* services and facilities; to *maintain and possibly increase the diffusion and quality of the services for the more vulnerable subjects*, such as the elderly, who are more exposed to being subjected to inhumane and degrading practices.

The opinion was drafted by Dr. Grazia Zuffa, Prof. Stefano Canestrari, coordinators of the work group which was established on 28 February 2014.

A number of experts were invited to give their professional advice on the subject during the plenary session, and a special thank you goes to: Dr. Piero Cipriano, consultant at the Servizio Psichiatrico di Diagnosi e Cura dell'Ospedale San Filippo in Rome and author of the volume *La fabbrica della cura mentale* (2013); Dr. Pietro Sangiorgio, Vice Secretary of the Coordinamento Nazionale di Servizi di Diagnosi e Cura, and once director of the Mental Health Department ASL RMH1; Prof. Maria Grazia Gian-

nichedda, lecturer in Sociology of political phenomena at the University of Sassari, President of the Fondazione Franco e Franca Basaglia and WHO expert in mental health and human rights.

The following also gave their contribution to the workgroup: Prof. Salvatore Amato, Prof. Luisella Battaglia, Prof. Carlo Caltagirone, Prof. Carlo Casonato, Prof. Antonio Da Re, Prof. Lorenzo d'Avack, Prof. Assuntina Morresi, Prof. Andrea Nicolussi, Prof. Laura Palazzani, Dr. Carlo Petrini, Prof. Monica Toraldo Di Francia.

Those who took part in the hearings and plenary discussion were also: Dr. Rosaria Conte, Prof. Andrea Nicolussi, Prof. Carlo Flamigni, Prof. Massimo Sargiacomo, Prof. Mario De Curtis, Prof. Giancarlo Umani Ronchi.

The opinion was voted unanimously by those present in the plenary session of 24 April 2015: Prof. Salvatore Amato, Prof. Stefano Canestrari, Prof. Bruno Dallapiccola, Prof. Antonio Da Re, Prof. Lorenzo d'Avack, Prof. Mario De Curtis, Prof. Riccardo Di Segni, Prof. Carlo Flamigni, Prof. Assunta Morresi, Prof. Demetrio Neri, Prof. Andrea Nicolussi, Prof. Laura Palazzani, Prof. Massimo Sargiacomo, Prof. Monica Toraldo Di Francia, Prof. Giancarlo Umani Ronchi, Dr. Grazia Zuffa.

The members without the right to vote expressed their approval: Dr. Carla Bernasconi, Dr. Rosaria Conte, Dr. Carlo Petrini.

Prof. Luisella Battaglia, Prof. Carlo Caltagirone, Prof. Cinzia Caporale, Prof. Carlo Casonato, Prof. Paola Frati were absent in the plenary session but endorsed the opinion at a later date.

1. Premise

In this document the National Bioethics Committee sets out to draw the attention of the institutions and public opinion to medical restraint, practised on patients in different typologies of socio-healthcare facilities in Italy. Restraint can be of a physical or pharmacological nature. In this opinion the ICB deals with the problem in particular of the form of restraint most giving rise to concern from both ethical and juridical points of view: mechanical restraint or the practice of forcefully restraining patients against their will. Hereinafter the term 'restraint' will be used to refer to this practice, without any other specification.

The practice of restraint is used for psychiatric patients in the Mental

Healthcare and Diagnosis Services (SPDC in Italy/MHDS in the English version of the opinion) of hospitals and private clinics; it is also used on minors with problems of mental or physical disability who are hospitalised or on the elderly in hospitals or nursing homes[37]. Particular attention is paid to the latter, owing to their vulnerability and because the rise in the average life expectancy has entailed a rise in invalidating illnesses and senile dementia, with massive recourse to institutionalisation. Since the context in which restraint is used and the motivations adopted to justify it are partly different for psychiatric patients and the elderly, the two questions will be examined separately. It must not be forgotten nevertheless that restraint, whether it be for the elderly or for psychiatric patients and the disabled, is deeply rooted in a common culture and healthcare tradition that pays little attention to the therapeutic relationship and the subjectivity of the patient.

2. The bioethical scenario

The ICB has already expressed its opinion on restraint use on several occasions, urging it to be overcome. This new opinion arises from the affirmation that, despite the intervening years, restraint is still widely used without any evidence of decisive efforts to reach a resolution and not even sufficient awareness with regard to the gravity of the problem.

Going in order, we can refer to the 2006 document, *Bioethics and the rights of the elderly*: in calling for the respect of the integrity of the elderly person and for nonmaleficence, the ICB stresses how "maleficence towards the elderly patient can amount to restraint, understood as the mechanical or pharmacological limitation of the possibility of an individual to move autonomously"[38]. With regard to restraint in a psychiatric context, the opinion *Psychiatry and mental health: bioethical guidelines*, of 2000, clearly states that "mechanical restraint must be avoided insofar as harmful to the dignity of the person". Such practice is considered a remnant of the asylum culture, which produces "a chronic condition rather than the recovery of the illness"[39].

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[37] For the subjects at a developmental age, see the report of the family associations quoted in the State-Regions document of 2010.

[38] ICB, *Bioetica e diritti degli anziani*, 20 January 2006, pp. 7-8.

[39] ICB, *Psichiatria e salute mentale: orientamenti bioetici*, 24 November 2000, p. 18.

The year prior to this in the document of September 1999, *The treatment of psychiatric patients: bioethical issues*, the ICB denounced "the frequent use of even prolonged restraint in most of the MHDS, the JPHs (Judicial Psychiatric Hospitals), and above all in private facilities (but often ones under the NHS)", pointing out that "such practices are in the first place against good medical-psychiatric practice". It was, thus, recommended that restraint and isolation should be"drastically reduced and practised only in exceptional cases should alternatives be lacking or in an emergency" and that anyway they should be limited in time, underlining at the same time "the convergence of the ethical norm of the respect for personal dignity and the clinical-therapeutic criterion"[40].

Also, the recent document *Dementia and Alzheimer disease: ethical issues* of 2014 analyses the questions of placement and involuntary treatment for these highly vulnerable people, stressing the connection between the rights of patients and an appropriate assuming of responsibility "since the lack and inadequacy of assistance for people with mental disorder leads to situations that are inhuman and degrading"[41].

In the bioethical debate on mental health, the passage to a new paradigm is therefore crucial to the substitution of the asylum approach; from a consideration of the mentally ill person as the victim of coercion and segregation (insofar as being socially dangerous) to the one of a suffering person to be taken care of, according to the principles and modalities of caring for patients which are the same as those used for other pathologies and affliction.

The overcoming of the "remnant of asylum culture" denounced by this Committee in 2000, means setting up psychiatric services that fully satisfy the ethical criteria that are generally recognised and applied in any other healthcare sector; from the commitment to offer treatment that might improve the quality of life (according to the principle of beneficence), to the obligation not to cause harm (principle of nonmaleficence), to the respect for the autonomy and dignity of the person (even when it is a question of deciding whether to medically intervene or not), to the respect of the criteria of justice in the allocation of resources.

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[40] ICB, *Il trattamento dei pazienti psichiatrici: problemi bioetici*, in "Council of Europe White Paper on the treatment of psychiatric patients", September 24, 1999.

[41] ICB, *Le demenze e la malattia di Alzheimer: considerazioni etiche*, June 20, 2014, pp. 18 *et seq.*

At the international level, there are many standpoints against coercion being used in psychiatry (in the context of which the issue of restraint is dealt with).

See the Recommendation by the Committee of Ministers of the Council of Europe on the protection of human rights and the dignity of persons with mental disorders, adopted in 2004, following the European White Paper (commented upon by the Italian ICB in the above mentioned opinion of 1999). In the recommendation, the questions of hospitalisation and involuntary treatment in psychiatric hospitals are addressed (as quite separate moments, Ch. III)[42], along with *seclusion* (the isolation room) and restraint (Ch.V, art.27), recommending the limitation of the measures to "cases of imminent danger for the person or for others and in proportion with the risks entailed", which must be written down in the person's medical record and in a special register. Note that restraint is addressed in a separate article as a completely separate measure from treatment.

Furthermore, the conclusive declaration of the conference of Helsinki, in 2005, signed by the health ministers of 52 countries of the European area of the WHO (*Facing the challenges, building solutions*) and the resolution of the European Parliament of 2006[43], known as the *Bowis Resolution*, calls for the respect of the human rights of persons with mental disorders (among which the right to autonomy is fundamental): to explicitly ask governments

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[42] Council of Europe, *Recommendation Rec (2004) 10 of the Committee of Ministers to Member States concerning the protection of human rights and the dignity of persons with mental disorders and its explanatory memorandum. Adopted by the Committee of Ministers on 22nd September 2004 at the 896th meeting of the Ministers' Deputies*, 22nd September 2004. The distinction between involuntary placement is based on the assumption that the presumption must avail in favour of the capacity to decide, even if the patient was admitted involuntarily, the presumption of competence to decide about his/her own treatment prevails, unless inability to decide on his/her own treatment was one of the legal criteria behind placement (see The White Paper and the ICB Opinion of 1999). With regard to the cases of involuntary treatment of the Recommendation: a serious danger to the person concerned and/or a serious danger to other persons; the treatment must have a therapeutic aim; other less restrictive treatment alternatives must not be available; the opinion of the person suffering from mental disorder must be taken into consideration. Criteria for the execution are also set out (e.g. the treatment must be proportional to the conditions of health; it must be part of a written programme; record of the treatment must be kept; it must be directed at the use of an acceptable treatment for the person as soon as possible; etc.) and their rights be upheld (e.g. the giving of information to the person or to their legal representative, communication and visits etc.).

[43] J. BOWIS, *On improving the mental health of the population. Towards a strategy on mental health for the European Union* (Bowis Resolution), 2006/2058 INI.

to "offer people with severe mental health problems effective and comprehensive care and treatment in a range of settings and in a manner which respects their personal preferences", and "to introduce or enforce mental health policy and legislation that sets standards that end inhumane and degrading care"[44]. On the specific subject of restraint, the *Bowis Resolution* takes the view that "any restriction of personal freedoms should be avoided, with particular reference to physical containment, which requires monitoring, verification and vigilance by democratic institutions responsible for upholding individual rights, in order to guard against abuses"[45]. Moreover, it believes "that the use of force is counterproductive, as is compulsory medication", recommending that all forms of compulsory medication should be with the authorisation of the appropriate authorities and used only as a last resort[46]. It is clear that these documents stress the close connection between therapeutic efficacy and the respect of the rights and dignity of the person[47]. The practice and culture of institutionalisation are condemned, since the lack of respect of rights is not only a violation of the person, but also one of the factors leading to the worsening of the mental pathology.

A clear connection can be noticed between the right to the autonomy of the person and the right to receive appropriate treatment, more precisely, the right to autonomy becomes the driving force of a valid and efficient therapeutic intervention. This has an important consequence with regard to the bioethical framework of restraint: in the case of the patient subject to mechanical restraint, there are no excuses for the violation of the person's autonomy in the name of their "wellbeing"; it is therefore not appropriate to assume two principles in conflict, the freedom of the person on the one hand, and the (supposed) therapeutic aim of the coercive practice (principle of beneficence) on the other. It is not so much a question of finding a balance between these principles, thus attempting to identify the situations in which

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[44] See The documents: *Mental Health Declaration for Europe, Facing the challenges, Building solutions*, (EUR/04/5047810/6) e *Mental Health Plan for Europe*, (EUR/04/5047810/7), WHO European Ministerial Conference on Mental Health, Helsinki, January 12-15, 2015.

[45] J. BOWIS, *op. cit.*, point 34.

[46] *Ivi*, point 33.

[47] See M. G. GIANNICHEDDA, *La salute mentale e i diritti della persona*, Laura Canovacci (edited by), 1978-2008: *Trent'anni di sanità fra bioetica e prassi quotidiane*, Commissione Regionale di Bioetica della Toscana, 2010.

the principle of beneficence may prevail over the right to autonomy of the patient (a position that runs the risk of institutionalising/regulating the violations of liberty)[48] as a question of confirming the principle that the use of force is always a violation of the person, with counterproductive effects. The fact that in quite exceptional situations the healthcare professionals can resort to justifications to apply restraint does not only disempower the rule of non-restraint but above all it does not modify the bases of the ethical discourse.

As also confirmed by the Danish Ethics Committee, in the significantly entitled document of 2012, *Power and powerlessness in psychiatry,* the principle stands firm that coercion invariably represents a violation, independently of the reasons for which it is applied. It must be remembered above all that restraint constitutes a hindrance to the relationship between physician and patient, which remains the main therapeutic instrument.

The use of force must nevertheless be avoided. This is a pressing invitation to the healthcare professionals involved at various levels in the giving of treatment, and is at the same time an appeal to the institutions for suitable policies to be drawn up.

This point of order is even more appropriate considering that, many decades following the psychiatric reform, and despite the numerous appeals to overcome restraint, it is still used in a non "exceptional" modality, as shall be seen below.

The above mentioned international documents point to a way to overcome the use of restraints, by means of the creation of area community services "that offer people with mental health problems choice and involvement in their own care, sensitive to their needs and culture"[49]. The above mentioned Danish Ethics Committee is also confident of a change in culture,

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[48] See C. PETRINI, *Ethical considerations for evaluating the issue of physical restraint in psychiatry*, Ann. Ist. Super Sanità, 2013, vol. 49, n. 3, pp. 281-285; See also F. MAISTO, *Imputabilità e vulnerabilità*, Quaderni di SOUQ - Centro Studi Sofferenza Urbana, 2011, No. 4. Scrive il giudice Francesco Maisto: "Si diffondono pratiche e protocolli ospedalieri e professionali sulla contenzione, nell'errato convincimento del valore giustificativo e tutorio per gli operatori in caso di lesioni, decessi e danni di qualsiasi genere ai pazienti. Tutti gli argomenti giuridici giustificativi di dette pratiche non tengono conto che nella legislazione vigente la contenzione in senso stretto, meccanica (distinta dall'occasionale ed eccezionale contenzione fisica e dalla contenzione farmacologia) non è prevista e che non trattasi di lacuna per distrazione del Legislatore, bensì di consapevole scelta dello stesso".

[49] Dichiarazione di Helsinki, *op. cit.* V, p. 4.

structured on two pillars: the recognition of the person as such, even before as a subject with an illness; and consequently, the consideration of the person "on an equal standing" with the medical staff (equal rights, equal dignity and the bearer of an irreplaceable "knowledge of himself/herself"). Such "equality" should foster a therapeutic relationship full of empathy and respect, so that the asymmetry of technical-scientific knowledge between patient and physician is not translated into a relationship of prevarication[50]. These are important recommendations in line with the community guidelines on mental health, aimed at defining and valorising the role of environmental and relational factors in treatment, in agreement moreover with the principles behind the Italian psychiatric reform.

The overcoming of restraint is thus interwoven with a new culture and organisation of services. This does not mean leaving the resolution of the problem to the change in culture, actually accepting a division between principles and practices and downgrading the former to moralistic proclamations as much as, on the contrary, departing from the refusal of restraint as the basis of "good practice", that is, an assumption to actually build a different healthcare culture, starting with an appropriate physician and patient relationship. This is the sense and value of initiatives such as the Mental Healthcare and Diagnosis Services which simply do not use restraint (*non-restraint*); or "restraint free" cities like Trieste, that are committed to avoiding restraining persons in all the socio-healthcare facilities of the city and the nursing homes for the elderly[51]. There are also examples of Judicial Psychiatric Hospitals in which restraint has been eliminated, like the one in Montelupo Fiorentino in 2012[52]. Moreover, the guidelines for the prohibition of restraint can be found in the healthcare programmes of a number of regions, as seen below.

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[50] Danish Council of Ethics, *The Danish Council of Ethics Statement on coercion in psychiatry*, p. 8.

[51] The initiative was begun by the Local Health Authority 1 of Trieste, in collaboration with the Medical Association. On December 21, 2013 the mayor of Trieste, Roberto Cosolini, launched an appeal to the mayors and healthcare representatives of Italy for the rejection of all forms of mechanical, pharmacological and environmental restraint which still today are used on weak citizens in violation of article 13 of the Italian Constitution.

[52] The director, Antonella Tuoni, thus stated her reasons for prohibiting restraint: "Tenere legata ad un letto una persona per giorni e giorni come pratica usuale richiamando l'articolo dell'Ordinamento Penitenziario che prevede l'impiego della forza fisica e l'uso dei mezzi di coercizione, ovvero la normativa in materia di trattamento sanitario obbligatorio, oltre che inumano è illecito" in "Ristretti Orizzonti", settembre 17, 2013.

The very existence of facilities that do not make use of restraint shows how the respect of the ethical principle, within an approach to care that places the physician and patient relationship between "equals" at the centre, might lead to good practices. One must, therefore one can.

3. The normative scenario

As well as representing the expression of a wide phenomenon, rich in facets in various fields of experience and human knowledge, under the legal profile the practices of restraint put the law scholars and lawyers before issues of great reach and considerable complexity.

In the light of this, a detailed study of the subject has been embarked upon in recent years – by virtue also of the importance of recent legal cases[53], which came to the attention of the newspapers in all their distressing aspects – by legal doctrines, particularly regarding constitutional and criminal law.

A brief outline of the various problem areas that have been pinpointed within the legal debate should therefore be given.

First of all, it must be specified that there are doubts concerning the very lawfulness of the use of restraints, particularly when they are used in the recourse to mechanical restraint: basically, the question must be asked whether one is facing legal acts, insofar as foreseen by the law, or whether they are prohibited acts (therefore illegal) and still in conformity with the legal system by the existence of a cause of justification determined each time.

As highlighted in literature[54], the question appears to be closely linked to the one concerning the exact limitation of the obligations coming into the healthcare provider's position as the upholders of human rights as set down in art. 40, par.2, p.c., in particular, the question must be asked whether

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[53] In particular reference is made to the cases of the deaths of Giuseppe Casu and Francesco Mastrogiovanni, for which see summarily and respectively, G. DODARO, *Morire di contenzione nel reparto psichiatrico di un ospedale pubblico: la sentenza di primo grado sul caso Mastrogiovanni*, www.penalecontemporaneo.it, June 12, 2013, and, by the same author, *Il nodo della contenzione in psichiatria tra gestione della sicurezza, diritti del paziente e "inconscio istituzionale"*, www.penalecontemporaneo.it, February 25, 2014.

[54] See the summary by C. SALE, *Analisi penalistica della contenzione del paziente psichiatrico*, April 27, 2014, pp. 8 et seq. available from www.penalecontemporaneo.it

among these obligations can be included the impediment of acts that are harmful to the patient and to others by means of restraint.

A first opinion, partly held by the doctrine and jurisprudence, states that the obligations regarding this also include the recourse to restraints, stating that they must be used whenever it is a question of avoiding direct self-harming or harm to others. Furthermore, similar conclusions would be valid after Law no. 180 of May 13, 1978, despite the abandoning – promoted by this very law – of the "custodialistic" model, strictly linked to the obsolete asylum approach of mental suffering on the basis of the presumption of the dangerousness of the patients.

Nonetheless, a different orientation of the doctrine and jurisprudence, valorising the absence of a specific set of regulations in the Italian legal system, has excluded the possibility of establishing a similar position for the mental healthcare professionals as the upholders of human rights, stressing how for these very reasons, also the general guidelines inferable from Law no. 180/1978 would provide in this sense[55].

According to this different reconstruction, mechanical restraint would in principle be open to embodying a criminal offence in accordance with arts. 605 p.c. (Kidnapping) and 610 p.c. (Private violence), but should be allowed when a cause of justification arises.

The justifying hypotheses identified in the doctrine are those in particular foreseen by art. 51 (Exercise of a right or fulfilment of a duty), art. 52 (Legitimate defence) or by art. 54 (State of need) of the penal code.

From this point of view, it is worth stressing that, setting aside the necessity to closely evaluate the assumptions and limits of applicability of all the causes of justification in question, the prevailing doctrine has privileged the application of the state of need and – should be the grounds for this - legitimate defence. This is above all on the basis of the argument whereby while the justification of the fulfillment of duty would lead to an asymmetrical concept of the care relationship, confining the role of the patient in a certain sense, the call for the causes of justification as laid down in arts. 52 and 54 p.c. on the contrary seems to draw from an equal

[55] There could be a doubt only with regard to the specific condition of the patient undergoing Compulsory Healthcare Treatment during hospitalisation.

interpretation of the same relationship, in this case more respectful of the patient's dignity[56].

Nevertheless, it must be remembered that in the case of mechanical restraint, the fundamental rights of the person are at issue. For this reason, the subject has also raised the problem, mostly addressed in Constitutional literature, of verifying the legitimacy in relation to the principles of the Charter of Fundamental Rights.

With regard to this, it has been highlighted how the problem must be seen in the light of arts. 13 and 32 of the Constitution[57]. Under this profile, the very nature of the restraint practices are in fact discussed: the question is far from being irrelevant and this can be deduced just by considering that while art. 13 concerns *coercive* practices, establishing the principle of the inviolability of personal liberty and foreseeing, in the fourth paragraph, punishment for any physical and moral violence "against a person subjected to restriction of personal liberty", art. 32 regards compulsory practices. At the discipline level, art. 13 foresees stricter limits than art. 32 of the Constitution: the latter establishes a so-called relative reserve, whereby "No one may be obliged to undergo any health treatment except under the provisions of the law", which "may not under any circumstances violate the limits imposed by respect for the human person" (2nd paragraph); on the other hand, at the same time art. 13 establishes a so-called absolute reserve and a so-called jurisdictional reserve, foreseeing in the 3rd paragraph that "No one may be obliged to undergo any health treatment except under the provisions of the law", which "may not under any circumstances violate the limits imposed by respect for the human person" (2nd paragraph), and that "In exceptional circumstances and under such conditions of necessity and urgency as shall conclusively be defined by the law, the police may take provisional measures that shall be referred within 48 hours to the Judiciary for validation and which, in default of such validation in the following 48 hours, shall be revoked and considered null and void".

Lastly, an intermediate solution is also assumed, which proposes a

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[56] For example, see G. DODARO, *op. cit.*

[57] M. MASSA, *Diritti fondamentali e contenzione nelle emergenze psichiatriche*, "Rivista italiana di medicina legale", 2013, pp. 179 and ss.

merging of restraint practices with compulsory healthcare treatment, suggesting their joint regulation by arts. 13 and 32 of the Constitution.

Independently of the case being examined, it has furthermore been underlined how it is nonetheless necessary – again from the point of view of constitutional legitimacy – that the possibility to use restraint on a mental patient must be foreseen by a law decreed by Parliament, ruling the premises for application[58].

In the Italian legal system no specific set of regulations is to be found: leaving aside arts. 41, par.3 of Law no. 354 of 26 July 1975, (Norms on prison rules on the enforcement of measures involving the deprivation and limitation of liberty) and 77 of the Regulation to which this refers[59], which regard the specific situation of the psychiatric patient in prison, the main normative reference still has to be identified – at least according to the majority of jurisprudential orientations – in art. 60, royal decree, 16 August 1909, no. 615 (Rules on asylums and the alienated, implementation of Law no. 36 of 14 February 1904). With regard to this latter measure, "[in] the mental asylums means of coercion of the mentally infirm shall be abolished or reduced to absolutely exceptional circumstances and cannot be used without the written authorisation of the director or a doctor of the institute. Such authorisation shall define the nature and duration of the means of coercion". Nevertheless, the present enforcement of art. 60 not only appears to be the subject of debate (since while the jurisprudence mostly tends to recognise its survival from the reform brought about by Law 180/1978, which says nothing on the subject, according to others it must be considered that it has been swept away by a tacit repeal), but even its very suitability to satisfy the relative reserve requested by the constitutional norms has been questioned, also when the one relative to art. 32 of the Constitution had to be

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[58] On this point, see also G. DODARO, *Il problema della legittimità giuridica dell'uso della forza fisica o della contenzione meccanica nei confronti del paziente psichiatrico aggressivo o a rischio suicidario*, "Rivista italiana di medicina legale", 2011, pp. 1499 et seq.

[59] Art. 41, par. 3 states: "No means of physical coercion shall be used that is not expressly foreseen by the regulations in force and, nevertheless, there can be no recourse to this for disciplinary aims but only to avoid causing harm to persons or things or to guarantee the safety of the subject himself/herself. Therefore its use must be limited to the time strictly necessary and must be constantly monitored by the physician". Art. 77 of the abovementioned legislation foresees the possible use of wrist and ankle cuffs, even though setting down a number of specific criteria.

dealt with, in fact, under this profile, the norm does not appear sufficiently structured and precise.

As can be seen therefore, (also) from the juridical point of view the use of mechanical restraints raises questions, even though limiting the view to a perspective anchored to the present normative situation, that are not easy to resolve and which need further reflection for its interpreters to reach full agreement. Nevertheless, it seems that some core issues can already be identified.

It must above all be stressed once again how – all the more so following Law 180/1978, but as can clearly be seen for reasons that are not limited to and prescind from this – a vision of the mentally ill patient as an allegedly dangerous subject and for whom care must be given in "custodialistic" forms can no longer be accepted. Hence, arises the need to understand the therapeutic relationship with the patients with mental disorders in terms which can superimpose those in any care relationship and, therefore, according to the fundamental criteria that are identical to those adopted for other pathologies and forms of suffering. In this sense, the National Bioethics Committee expresses its hope that the physician-patient relationship can be conducted on an equal footing, fully respecting the canons of a human relationship inspired by the equal dignity and liberty of the subjects involved.

Consequently, any recourse to mechanical restraining techniques must represent the extrema ratio and it has to be considered that even in Compulsory Healthcare Treatment they can be used only in situations of real need and urgency, proportionately to the actual demands, using the least invasive modalities and only for the time necessary to overcome the conditions making them necessary. In other words, it is not sufficient for the patient to be simply in a state of agitation for restraints to be "justified" but there must be a "serious and immediate" danger that the patient commits self-harm or harm to others. When the patient ceases to pose this risk, the restraining treatment must stop as it would no longer be justified by need and would add to the offences mentioned above.

Lastly, these guidelines seem to represent useful and, in some respects, inalienable points of reference for a more appropriate application also of forms of restraint different from the mechanical one, as long as opportunely restricted in the respective situations and specific circumstances.

4. Restraints in the Mental Healthcare and Diagnosis Services: research guidelines

As mentioned above, the different forms of physical and pharmacological restraint must be distinguished. Mechanical restraint is a type of physical restraint but there are other forms of physical restraint which are quite different from the mechanical one. *Holding* is one of these, a technique used by the healthcare professional to restrain the patient's crisis, talking and listening to the patient and using their own body in an attempt to establish a dialogue. In this case, the use of force and physical limitation of the person are contingent, of short duration, useful for creating the relationship, keeping the negotiation open in the search for solutions and shared choices. *Holding* can thus represent one of the *de-escalation* procedures during the crisis management of aggressive patients, which are alternative to mechanical restraints (with the objective of restraining – in the sense of understanding and "keeping inside oneself" the patient's experiences – alleviating their anger and suffering).

Mechanical restraint is different and is carried out by using a straight jacket, restraining beds, wrist and ankle straps. *Seclusion* is another method used, or the closing of the patients in isolation cells. It is mainly used in Anglo-Saxon countries, unlike in Italy where mechanical restraint is usually preferred.

As far as pharmacological restraint is concerned, this consists in the giving of drugs in higher doses than those prescribed in the current therapeutic guidelines, aimed at the dulling of the patient's will and reactions. Pharmacological sedation undoubtedly represents an instrument to deal with the crisis management of aggressive patients, but that does not mean that it is opportune to substitute mechanical restraint with a pharmacological one. In fact it is evident that the high drug dosages for restraining purposes can have risky side effects, as well as delaying the start of the therapeutic relationship which is an indispensable resource towards recovery. For this reason in the healthcare programmes and guidelines of a number of regions it is recommended to keep to the correct dosages of sedatives and to carefully monitor any recourse to improper posology, which should anyway be limited in time.

Lastly, in the Mental Healthcare and Diagnosis Services that choose not to restrain patients or to limit such practice to a minimum, more intensive

use of psychotropic medications with respect to the services resorting more heavily to restraint is not evident from the data available[60].

The underlying issue is that it is the orientation of the service that makes the difference. Therefore, the solution lies not so much in the substitution of pharmacological restraint with mechanical restraint, as in the overcoming of the very culture of restraint, making proper use of all the therapeutic instruments, drugs included.

Mechanical constraint can be called the "remnant" of psychiatric healthcare. In 1978, the law for psychiatric reform decreed the end of new admissions to asylums and the course towards their closure begins; the new system of area responsibility is set up, delegating acute cases to the Mental Healthcare and Diagnosis Services in the general hospitals. There is no reference to restraint in the psychiatric law, nor is the problem dealt with at a later date as urgently and seriously as it should have been in the healthcare programmes and other mental health guidelines, as will be examined below.

Even more surprising is the lack of research and the absence of systematic monitoring of such a physically invasive and harmful practice, despite the appeals for the above mentioned methods to be overcome. Restraint generally becomes the subject of public debate when a person being restrained dies in tragic circumstances, with the consequent investigation by the judiciary. This happened in 2006 when the death of Giuseppe Casu, who had been tied to a psychiatric ward bed for seven days in the Cagliari hospital, fuelled the protest of the associations of patients families and the indignation of public opinion; in 2010, Francesco Mastrogiovanni died in Vallo di Lucania after ten days of continuous restraint. In this case too the role of his family, the promoters of the Committee "Verità e Giustizia per Francesco Mastrogiovanni", was fundamental in informing and raising public opinion awareness.

Despite the poor level of research on the subject, there are some Italian

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[60] Data from the SPT study, a longitudinal survey by the Istituto Mario Negri of Milan on 61 area services and 39 MHDS of 12 regions on the results of serious mental disorders over five years from its being set up; see G. CARDAMONE, A. GUARNIERI, L. MARI, *Una elaborazione critica dei dati sui SPDC. Riflessioni sul senso della crisi e del ricovero in psichiatria,* "Rivista sperimentale di Freniatria", 2003, Vol. CXXVII, supplement No. 2, pp. 23-24. The authors also point out that services that make less use of restraint do not have a larger personnel than the others. See also P. CIPRIANO, *La fabbrica della cura mentale*, Eleuthera, Milano 2013, p. 51.

and foreign studies that give an overall picture of the working of services in which the use of restraint is included[61].

Progres Acuti, some research carried out between 2002 and 2003, made it possible to gather national data on the characteristics and operational models of the 262 Mental Healthcare and Diagnosis Services running in Italy and the 16 area Mental Health Centres open 24 hours a day (able to treat patients with acute mental health crises): during this period, there was a 12.9% Compulsory Healthcare Treatment rate. 80% of the MHDS are not open, while 15 MHCs out of 16 are open 24 hours a day. The "closed door" model is more widespread in Italy with respect to abroad[62]. However, at the national level, the number of patients who have undergone mechanical restraint is not known, nor is the number of restraints or the total number of hours of restraint over a yearly period.

A more exhaustive picture is given at the regional level by the research on MHDS of metropolitan area of Rome, edited by the coordination of the Lazio Mental Healthcare and Diagnosis Services, which began in 2005 with a successive follow up[63]. This study made it possible to monitor the use of mechanical restraints in that period, understanding the reason for their use, identify their evolution and put forward solutions; this is all the more important insofar that it concerns a large metropolitan area, with a variety of old and new mental health issues. They are reflected on the activities of the MHDS which have to deal with all sorts of urgent cases (psychopathic behaviour, co-diagnosis of addiction and mental disorder, emergencies linked to the new social poverty and crises).

23 (out of 24) MHDS took part in the first step of the Lazio research, in the four months from January to April 2005: of these only one of the MHDS at the San Giacomo hospital in Rome did not use restraint[64].

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[61] The studies mentioned below have been outlined and debated during the ICB hearings.

[62] DELL'ACQUA *et al.*, *Caratteristiche e attività delle strutture di ricovero per pazienti psichiatrici acuti: i risultati dell'indagine nazionale Progres-Acuti*, "Giornale Italiano di Psicopatologia", 2007,13, pp. 26-39.

[63] P. SANGIORGIO, *La prevenzione, la gestione e, in prospettiva, l'eliminazione della contenzione nelle emergenze psichiatriche dell'area metropolitana di Roma*, in P. SANGIORGIO and G. M. POLSELLI (edited by), *Matti da (non) legare*, Alpes, Roma 2010, pp. 1-40.

[64] Moreover this service no longer exists, the hospital centre was closed under this Region's rationalisation programme.

Out of 3,130 patients admitted to the centres in that period, 297 were restrained, corresponding to about one out of ten, with some being restrained more than once. The restrained patients were subjected to two restraining interventions on average, with a maximum number of 12 restraints per single patient (the total number of restraints was in fact 581). The average number of restraints was 26 per service, with a large variability; apart from the San Giacomo hospital which used none at all, the figures range from a minimum of 5 restraints in 4 months to a maximum of 71.

The average duration for restraint was about 14 hours, ranging from 20 minutes to 216 hours: this means that a person was restrained for 9 consecutive days.

The average duration of the restraint per patient was 23 hours, varying from a minimum of 8 hours to a maximum of 62 hours.

The number of restrained patients is surprising despite being under Compulsory Healthcare Treatment, and subject to procedures for the upholding of individual rights foreseen by the law: in 34% of the cases the patient was strapped down simply in accordance with art. 54 of the penal code (due to "state of need").

With regard to the motivations: most of the patients (48%) were restrained due to psychomotor agitation, 37% due to other-directed aggressiveness, 9% to self-harm, 7% to risk of escape, 3% to refusal of treatment and 13% due to states of confusion of organic, toxic or pharmacological origin.

In a comparison with other countries in areas with metropolitan features that can be considered on a par with those of Rome, the following emerges: from the study carried out in 2000 on 50 emergency psychiatric units in New York, it appears that the rate of restrained patients out of those discharged from care is 3.1%, for an average duration of 3.3 hours. The comparison therefore puts Italy in a bad light, since in the survey on the Lazio Region there is a rate of 9.48 restrained patients out of 100 discharged, with a rather higher average duration of restraint (14 hours).

This rather poor data does however offer some interesting considerations. Firstly, one cannot say that mechanical restraint is an exceptional practice and a last resort, if it is true that on average 10% of the patients admitted for acute mental health crises is restrained, all the more so if the services over the average are considered, which reach peaks of 23, or 25%. Also the data on the commonly adopted reason to justify the use of restraint,

"psychomotor agitation" (a somewhat general term), suggests that it is not an "extreme" intervention at all. Lastly, the very fact that the healthcare providers are not requested to give more precise motivations and more convincing justifications reneges the routine nature of the practice.

Furthermore, the data on the duration of restraint is cause of concern, since the strapping down of a person for such prolonged periods does not seem to be in keeping with the "immediacy" of "danger of serious harm", as per art. 54 of the p.c., often used by the professionals to justify their decision to restrain (see the paragraph on the juridical standpoint).

Moreover, the significant variability in the use of restraint in services, which also insist on areas having similar features and types of usage, suggests that the culture and organisation of the services play a decisive role in the use of restraints rather than the typology of usage.

The primary role of the approach of mental health services is confirmed by other surveys conducted abroad; in the Commission's report on the quality of treatment in the State of New York for the evaluation of psychiatric care in hospital environments of 1994, it is stated that the differences in the rates of restraint use are not so much correlated to the characteristics of the patients, as to the "philosophy" of the services[65].

5. *Restraint* and *non-restraint* culture

The above mentioned Italian SPT study (Area Psychiatric Service) makes it possible to understand the different approaches of the services. From the examination of a sample of 39 MHDS and two university clinics from all over the country, it can be seen that in only 12% of the services mechanical restraint is banned by choice. Among the remaining ones, restraint is somewhat a rare event in just one third of the cases, while in one third it is quite a frequent practice, with peaks of up to thirty restraints in the last month. Patients admitted to a psychiatric unit voluntarily are also subject to restraint and 42% of the MHDS examined does not transform voluntary admission into CHT when it is decided to restrain the patient, letting it pass as "normal" practice, which does not interrupt the voluntary nature of the

[65] NYS Commission on quality of care, *Restraint and seclusion practices in New York State psychiatric facilities and voices from the Frontline: Patients Perspectives of restraint and seclusion use*, 1994.

admission. Moreover, in 64% of the MHDS using restraints no record of the cases is kept[66].

The MHDS that use restraint have "weak" regional services and socio-healthcare networks behind them; that is, area services open for a limited number of hours without a sufficient variety of staff, with poor links with other centres and services of the local socio-healthcare network. Furthermore, restraint is accompanied by a series of other practices limiting the patient's freedom of choice, like the taking away of personal belongings, the obligation to wear pyjamas, the limitation of visits by family members and telephone calls, the rationing of cigarettes etc.

Instead, the *non-restraint* MHDS have community services that are open all day or 24 hours a day, hence with a good emergency filter capacity made even more efficient by the fact that the local healthcare providers already know the person who arrives during a crisis, and in turn the patient is less afraid when received by staff already familiar to him or her.

In commenting on these data the researchers focus the attention on the correlation between restraint and aggressive practices, such as body search and others already mentioned. In units that opted for non-restraint, no restrictive practices are used. Hence the conclusion: "Since it is not credible that the seriousness, behavioural expressiveness and the psychopathological profile of the patients admitted by these services are different", it is the approach to work of the healthcare providers and the services system operating in the regional hospital service that makes the difference[67]. Lastly, as already shown, it does not appear that the *non-restraint* MHDS make recourse to a greater use of drugs with respect to the *restraint* ones.

6. Reasons for not restraining

Despite the fact that the research carried out in Lazio shows that only a part of the restraints is decided by the healthcare providers in order to

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[66] G. CARDAMONE *et al.*, *op. cit.*, p. 23.

[67] E. TERZIAN, G. TOGNONI, *Indagine sui servizi psichiatrici di diagnosi e cura*, "Rivista sperimentale di Freniatria", 2003, vol. 127, suppl. n. 2, pp. 3 et seq.; M. G. GIANNICHEDDA, *La democrazia vista dal manicomio. Un percorso di riflessione a partire dal caso italiano*, "Animazione sociale", April 2005, no. 4, pp. 19-31.

deal with the patient's aggressiveness, the reasons more commonly given regard the safety and management of the conflict with the patient.

It is important to stress that international research also confirms this contradiction. Data from the United Kingdom offer a similar picture to the Lazio one: only 44% of the cases concern patients strapped down due to their confrontational actions. Furthermore, in many cases the choice to use restraints decreases safety instead of furthering it; preventive or reactive restraint can generate or exacerbate conflicts with patients, as often happens when a person is tied down to be given medication or when it is decided to preventively restrain patients who have committed acts of aggression. On the contrary, treating the patient with respect and a "normalised" management of the service, starting from the "open doors" practice as in other units, contributes to create a more serene atmosphere, promoting the reduction of aggressive and self-harming behaviour[68].

In the United Kingdom an attempt has been made to draw up a new conflict management model in psychiatric wards, analysing different operational models. A key factor of the new model lies in the attention to rights, starting from the giving of information to the patient and the possibility for them to express their point of view and file complaints. "The attention to the procedure for the upholding of the rights, information and the requests of the patients could increase the legitimacy of the psychiatric ward, strengthen the patients self-esteem, suppress or decrease anger, contribute to lowering the conflict and reducing the restraint rates". The model is based on a normative framework that is concerned with rights and which fosters a care approach where there is room for "the listening, negotiation, flexibility, compromise"; these are all useful elements in reducing conflict. Conflict management is thus part of a general direction towards the respect for the autonomy of the person, which is reconfirmed in all the stages of recovery: giving space to the choices of the patients for food, schedules and the taking care of personal belongings. Lastly, the staff is asked to intervene to try and "reply to the loss of faith and hope and self-stigmatisation of the persons following admission to a psychiatric facility"[69].

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[68] L. BOWERS, *On conflict, containment and relationship between them*, "Nursing Inquiry", 2006, 13, 3, pp. 172-180; P. SANGIORGIO, M. POLSELLI, *Matti da non legare,* 2010, *op. cit.,* p. 8.

[69] L. BOWERS, *Safewards: a new model of conflict and containment in psychiatric wards*, "Journal of Psychiatry and Mental Health", 2014, 21, p. 507.

To summarise, there are various reasons of an ethical nature not to restrain, along with those of safety, prevention and good services management; non-violent and non-coercive management in MHDS eliminates the atmosphere of fear (for patients and healthcare professionals) and reduces stigma. There are also therapeutic reasons, first of all so as to avoid compromising the therapeutic relationship by means of a vicious circle that physical restraint triggers off; the agitation of the restrained person is aggravated and higher doses of sedatives are needed, with the result that their state of confusion worsens, in turn reducing the communication between them and staff.

These therapeutic principles are at the basis of the model of community psychology and psychiatry, but they have even more ancient origins. It suffices to mention the concepts of the psychiatrist John Conolly, expressed in 1856: if it is allowed to restrain hands and feet, in a short time there will be a total process of regression in the patient and there will be the start of all sorts of neglect and tyranny, "until the repression becomes the usual substitute of attention, patience, tolerance and correct management"[70]. In other words, the respect of the person qualifies the assistance and is the measure of the professional skills of the healthcare providers.

7. Strategies of change

The idea that by means of a change in the culture and organisation of services one can significantly influence restraint is confirmed by the outcome of the initiatives aimed specifically at this. This was the case in the Danish project, National Breakthrough Project on Coercion in Psychiatry, adopted in 27 psychiatric wards in all, from August 2004 to June 2005. In the final report of the project, it says that a change has begun and there was greater attention by staff to dialogue and the involvement of the patients. With respect to the number of coercive episodes, these had decreased by 20% in 33% of the wards taking part in the project, while 8% of the services had achieved over 50% fewer coercive practices[71].

Positive signs also come from the monitoring carried out through the follow-up of the research on MHDS in Lazio from 2005 to 2011. In the space

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[70] J. CONOLLY, *The Treatment of the Insane without Mechanical Restraints*, 1856; P. CIPRIANO, *La fabbrica della cura mentale*, Eleuthera, Milano 2013, p. 50.

[71] Danish Council of Ethics, *op.* cit., p. 7.

of six years, the number of restrained patients decreased by one quarter. The average number of restraints for MHDS also went down, just as the average number of hours of containment per service did. Instead, there was no reduction for the average duration of restraints, which in fact increased[72].

This shows that the setting up of specific programmes along with the simple attention to cases of restraint through monitoring can achieve positive results, increasing the level of awareness of healthcare providers with regard to the extreme meaning of containment as the violation of a right. This is even more true in Italy, where it appears that not always is the use of restraint noted down by the physicians in medical records.

Healthcare providers are therefore asked to use more thoroughness, in the respect of the ethics of care and in the upholding of the law. It must be remembered that a recent first instance judgement defined the narrow limits of the lawfulness of the practice, clearly stressing that – even though having to recall the ongoing debate on the subject in legal doctrine – mechanical restraint is an unlawful act of healthcare in itself (since, it follows that, it can be allowed, insofar as being "exceptional, episodic and contingent", should a cause for its justification arise); furthermore, it highlighted the fact that "the gravity, plurality and temporal extension of mechanical restraints in an MHDS mark a consolidated contrast between usual practice and norms of the state in force"[73].

It is the duty therefore of the healthcare professionals to always note down the decision to strap down the patient in their medical record. Not only: the reasons and the context of the cause for justification advocated each time must be specified in full detail.

The institutions are also called upon to play their part, particularly the Regions in charge of local healthcare services. It is also necessary to give clearer guidelines. At the national level the document *Physical restraint in psychiatry: a possible prevention strategy*, approved by the Conference of Re-

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[72] The average number of cases of restraint has gone from 92 in 2005 to 57 in 2011, while the average number of hours of restraint per MHDS has gone from 1,500 hours to 999 (from the consultation by Pietro Sangiorgio).

[73] Grounds for the first instance judgement in the trial for the death of Francesco Mastrogiovanni, filed April 27, 2013/T. Vallo della Lucania, October 30, 2012 (filed April 27, 2013), in www.penalecontemporaneo.it.

gions on 29 July 2010, contains a series of recommendations, the first of which regards the monitoring and systematic collection of information on the phenomenon of restraint (duration of restraint, night time restraints, the frequency of restraint episodes, the number of patients restrained, the diagnoses associated with the use of restraints). The data flow from the Departments of Mental Health should merge together at central regional level, so as "to represent an instrument for the observation of restraint as a sentinel event". Other recommendations of the document concern the monitoring of violent behaviour, the training of staff to deal with critical situations, the definition of facility and operating standards for the management of violent acts, the monitoring of the organisation model in its impact on the number of restraint episodes, the ascertainment of crisis management, the fostering of the "transparency of care facilities so as to improve accessibility, liveability, the acceptance of service and to facilitate communication with the outside".

Even though many of these recommendations make very good sense, they are nonetheless too generic on some points and on the whole do not appear sufficient to give a clear sign towards the overcoming of restraints.

This is confirmed by the fact that the guidelines of the various regional programmes differ quite significantly; from Tuscany, which in its 2012-2015 healthcare and social programme, reconfirms "the absolute prohibition of any form of physical restraint whatsoever" within the MHDS whose doors "must stay open" and recommends "constant attention to the appropriateness of the recourse to pharmacological therapy"[74], to the Lombardy regional mental health programme 2004-2012, which interprets the document of the Regions as an invitation to "regulate" the practice of restraint, referring to protocols at the hospital level, both for the use of restraint in a psychiatric and non-psychiatric context, "even though recognising the extraordinariness of the recourse to restraint, but at the same time aware of the incidence of the phenomenon in general"[75]. An examination of the guidelines on restraint of the Niguarda hospital, one of the biggest in Lombardy, highlights the ambiguity of the regula-

[74] Social healthcare programme 2012-2015 of the Region of Tuscany, p. 181.
[75] Regional Mental Health programme 2004-2012 of Lombardy, pp. 156 and 158.

tions. From the very premise the document acknowledges that restraint is a practice that is "more frequent than could be thought"; nevertheless, it chooses to stress in the first instance "that mechanical restraint can be made necessary in various stages of different mental pathologies", rather than underlining the reasons (of an ethical and therapeutic order) for "not applying" restraint[76].

Other passages of the guidelines are even more interesting, as they implicitly bear witness to the widespread and indiscriminate use of restraint. In the paragraph entitled "Research and the use of alternative solutions", a long and varied list of "situations and high-risk behaviour which is usually dealt with by using physical restraint": these range from anxiety disorders, to psychomotor agitation, to delirium and hallucinations, to changes in the sleep-wake cycle, the prevention of falls and even (pharmacological) therapeutic treatment. It is evident that many of these situations – for example anxiety disorder and changes in the sleep cycle – do not seem to satisfy the requirement of a state of need and urgency. To simply consider that "the search for other solutions is to be hoped for" in the "risk behaviour" listed, as stated in the Niguarda guidelines, is a message that does not do any justice to the gravity of the problem[77].

The appeal made to the Regions to monitor the phenomenon, as already stated in the 2014 Regions document, becomes even more urgent in the presence of the habitual recourse to restraint. A national monitoring institution should be set up, with the pooling of regional data so as to be able to compare regional policies and overcome the disparities.

Programmes should also be promoted and financed to evaluate the progress in mental-healthcare, clearly establishing the non-recourse to restraint as a quality factor in services evaluation.

The American approach to this is worth mentioning here, where stricter limits in the use of restraint and isolation constitute quality factors in the

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[76] The above mentioned ambiguity is also to be found in other crucial passages of the document. On the one hand, it seems that restraint is considered possible only for violent patients, so much so that great emphasis is placed on the identification of the "patients at risk" of aggressive behaviour; on the other hand, a series of different disorders are listed "which are unusually dealt with physical restraint" and which have nothing to do with violent behaviour (see below).

[77] Azienda Ospedaliera Ospedale Niguarda, *La contenzione fisica in ospedale*, Evidence based Guideline, 2006 (reviewed in 2008), pp. 4-10.

evaluation of the service and represent an obligatory requirement for the establishments wanting accreditation[78].

8. Restraints and the elderly

It has been said that the subjects most exposed to the use of restraints are mental patients and the elderly. The latter are an even greater cause for concern, not only owing to the high number of elderly patients and therefore the possible recipients of restraint but also because the practice is passed over and forgotten to an even greater extent than with psychiatric patients. In a psychiatric context restraint was debated at the time of the outdating of asylums, even if not sufficiently so, since due attention was not (and is not) paid to the survival of the asylum culture. The debate on the elderly on the other hand is much more lacking.

There are many forms of mechanical restraint for the elderly, aimed at limiting the freedom of movement of the whole body or parts of it: from bracelets to immobilise wrists and ankles, to chest straps to block the patient to the bed or wheel chair, to pelvic straps, corsets with braces or pelvic belts; wheelchair trays, various types of straitjackets, like the "safety vests", that are worn like a vest garment leaving arms and hands free but at the same time stopping the person from getting out of bed, and finally the "four-side rails" (uprights on the bed).

The list of restraint techniques has been given since their mere description gives an idea of the amount of suffering they can cause and how harmful to the dignity of the elderly person they can be. It must be stressed that many of these instruments have been devised to enhance the possibility of movement and action and not to limit it; this is the case of the "serving tray", designed to enable the person confined to a wheelchair to eat their meals but which instead is often used to stop them from getting up autonomously and walk around.

Pharmacological restraint is also used, which amounts to a restraint

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[78] In particular, in 2000, the *Joint Commission on Accreditation of Healthcare Organizations* (JCAHO) decided to apply the "one hour rule", according to which the facility applying for accreditation must see that patients subjected to restraint or seclusion are examined within one hour by an independent physician for an assessment of the suitability of the measure adopted, in "*Psychiatric News*", October 6, 2000.

when the drugs acting on the central nervous system are aimed at limiting or suppressing the movement capacity and interaction of the person. These are often sedatives, antidepressants and antipsychotic drugs which, in excessive doses, have many side affects, such as drowsiness, confusion and agitation. Pharmacological restraint is often used together with a mechanical one[79].

The use of restraints is worsened by the fragility of the elderly. The increase in life expectancy does not yet correspond to an improvement in the quality of life, and most elderly people have invalidating illnesses and senile dementia in the last 3/5 years of life, these are the patients affected most by the use of restraints.

9. The spread of the use of restraints in residential care facilities and hospitals

As stated above, the phenomenon is deeply rooted and the data quite poor. In a survey carried out in Italy, big differences are to be seen from region to region. The spread of restraint is confirmed by the fact that in many areas guidelines and operational procedures have been drawn up[80]. In 2006 research was carried out in the province of Trieste on 44 facilities for the elderly out of 100 present in the area. At the time of the research, 63% of the patients were fully or partially self-sufficient. 18 facilities out of 44 claimed that they used restraint, while 19 did not, even if in a more in-depth survey a number of *restraint* measures were found to be used such as tray tables and drug overdose.

Foreign data also shows that the recourse to restraint is frequent and for prolonged periods, especially in hospitals[81].

As far as concerns the variables correlated to the non-restraint facilities with respect to those using restraint, not only does the seriousness of the

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[79] L. BICEGO, *Luci ed ombre sulla contenzione alle persone fragili*, in M. MISLEJ, L. BICEGO, *Contro la contenzione*, Maggioli Editore, Santarcangelo di Romagna 2011; M. MISLEJ, L. BICEGO, *Assistenza e diritti. Critica alla contenzione e alle cattive pratiche*, Carocci Faber, Roma 2007.

[80] For example, see E. ZANETTI, S. COSTANTINI, *Uso dei mezzi di contenzione fisica*, Gruppo di Ricerca Geriatria di Brescia, 2001.

[81] See O. J. DE VRIES, G. J. LIGTHART, T. NIKOLAUS, (on behalf of the participants of the European Academy of Medicine of Ageing-Course III), *Differences in period prevalence of the use of physical restraints in elderly inpatients of European hospitals and nursing homes [Letter]*, "Journal of Gerontoly Medical Sciences", 2004, 59A, pp. 922–923.

state of health have a bearing on this but also the approach of the nursing staff to restraining patients[82]. The training and professional skills of the staff are stressed as being key factors and more important than the actual number of personnel; in a study on 15,000 nursing homes, differences in the number of personnel between *restraint* and *non-restraint* facilities did not come out[83].

On this basis, a number of countries went ahead with regulatory action to protect the more vulnerable patients from abuse, especially the elderly. America has the *Nursing Home Reform Act* of 1987 which contains a charter of rights of persons in nursing homes, among the rights listed stands out the right to "be free from physical restraint"[84].

Furthermore, there is evidence of the harmfulness of restraining practices not only due to the immediate effects, but also the long term ones: restrained subjects suffer from loss of autonomy, a reduction in activity, an increase in morbidity and mortality[85]. The negative effects not only affect the individuals that are restrained but also the general atmosphere of the homes or wards, owing to the fear and bewilderment of the other patients who anticipate similar treatment.

10. Conclusions and recommendations

The ICB takes the opportunity to stress the general lack of attention with regard to the use of restraint, and in particular to mechanical restraint, which is still used in a non "extraordinary" way. This is even more serious as the aim to overcome the use of restraint is not new and has for some time now been expressed at different institutional, national and international levels, not least in the above mentioned ICB document of 2000. This is even more worrying in as

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[82] See for example the study of 33 nursing homes and 12 residential units in Sweden for elderly dementia sufferers: the 540 residents, of an average age of 82 and the 529 carers were evaluated in order to identify the environmental features affecting restraint (S. KARLSSON, G. BUCHT, S. ERIKSSON, P. O. SANDMAN, *Factors relating to the use of physical restraints in geriatric care settings*, "Journal American Geriatric Society", 2001, 49 (12), pp. 1722-28.

[83] N. G. CASTLE, B. FOGEL, *Characteristics of nursing homes that are restraint free*, "Gerontologist", 1998, 38, pp. 181-188.

[84] N. G. CASTLE, V. MOR, *Physical restraint in nursing homes: a review of the literature since the Nursing Home Reform Act of 1987*, "Medical Care Research and Review", 1998, 55, 2, pp. 139-170.

[85] See the retrospective study on 122 deaths during restraint: 78% were women, of an average age of 81. The victims died while they were strapped to a chair (42%) or to the bed (58%). 83% of deaths took place in nursing homes.

much as the available research, even though insufficient, highlights the fact that the orientation and culture of the services influence the choice of whether to use restraints or not rather than the behaviour and characteristics of the patients. This shows that the use of restraints can be avoided and the presence of wards where restraint instruments do not even exist bear witness to this.

In this framework the ICB:

- Stresses the need to overcome the use of restraints, in the context of the fostering of a care culture that respects the rights and dignity of persons, especially those who are more vulnerable.

- Condemns the present widespread use of restraints. It is true that the possibility to use mechanical restraint has never been completely excluded. Nevertheless this should be interpreted as a caution, with respect to any extreme situations of jeopardy that the healthcare professionals are unable to deal with in any other way. Instead, this absolutely exceptional "emergency exit" – as it could be defined – which allows staff to depart from the regulation not to restrain patients against their will, has all too often been converted into routine practice. Tolerance, granted in extreme cases for an intervention that is so harmful to the freedom and the dignity of the person, has been wrongly interpreted as a licence for its standard use.

- Reminds the carers of sick persons, but also the competent healthcare bodies that the use of force and mechanical restraints represent a violation of the fundamental rights of the person. The awareness of this violation, with the responsibility deriving from it, should guide the daily actions of the healthcare providers and be a stimulus to the institutions to urgently adopt all possible measures to reach the objective of overcoming the use of restraints.

The ICB thus urges the regions and government to:

- Increase research on restraints in relation to the organisation and culture of the services, particularly as far as concerns the elderly who are the most defenceless subjects in the face of coercive practices.

- Start a careful monitoring of the phenomenon, at the regional and national level. This requires constant attention being paid to the daily practice in the wards; in particular, the healthcare professionals are asked to use extreme accuracy in recording the cases of restraint, the specific reasons for choosing to strap down the patient, the duration of the measure. A role of surveillance, prevention and cultural promotion shall be reserved for associations and family associations in particular.

- Set up programmes aimed at overcoming of the use of restraints in the context of the fostering of a general treatment culture that respects rights, taking action on the organisation models of the services and the training of personnel.

- Use the evaluation instrument to foster innovation, introducing quality standards promoting non-restraint services and facilities.

- Pay the greatest attention, during cuts in healthcare and the social services, to maintain and possibly increase the diffusion and quality of the services aimed at more vulnerable subjects, insofar as being more exposed to inhumane and degrading practices.

Presidenza del Consiglio dei Ministri



MOTION

THE IMPORTANCE OF IMMUNISATION

24 April 2015

It is an alarming fact that the decrease in immunisation coverage has brought about a considerable rise in the cases of measles worldwide. In Italy alone 1,686 cases were reported in 2014, the highest number in Europe. Even the WHO has explicitly urged Italy to take measures against this outbreak. Moreover, various cases of meningitis, some even fatal, have been recorded in different regions. The ICB has taken note of these data and stresses its deep concern about the increasingly widespread tendency to defer or even to refuse the compulsory vaccinations which are recommended by the Healthcare Authorities and universally recognised as being efficacious.

With regard to this phenomenon, the ICB stresses[86] how vaccinations are one of the most efficient preventive measures, with a particularly positive risk/benefit ratio, having not only an important healthcare value but also an intrinsic ethical one.

Consequently the ICB considersd it urgent to call the attention of the Italian society to the value of assuming personal and social responsibility and invites the Government, the Regions and the competent institutions to make an increased effort so that both mandatory and recommended vaccinations might achieve appropriate immunisation coverage (95%). In particular it is necessary to mobilise the doctors and healthcare facilities of the region and promote effective information, communication and education campaigns aimed at stressing the importance of immunisation at the individual and collective level and to draw citizens attention to making conscious responsible choices in their own interest. With regard to this, the spread of falsehoods and prejudices cannot but be stigmatised, for example those concerning the existence of a presumed correlation between vaccinations and the rise of autism, an hypothesis that has been dismissed of any scientific foundation, as has been once again demonstrated in a recent study[87].

It must be remembered and stressed that for reasons of proven safety

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[86] See ICB, *Le vaccinazioni*, September 22, 1995.

[87] A. JAIN *et. al.*, *Autism Occurrence by MMR Vaccine Status Among US Children With Older Siblings With and Without Autism*, JAMA (The Journal of American Medical Association) 2015, 313 (15), pp. 1534-1540. It must be remembered that the scientific publications that claimed a link between vaccinations and the onset of autism have been withdrawn and that the main author of such thesis has been charged with fraud.

and efficacy, vaccinations are numbered among the measures to which priority has to be given in the planning of healthcare coverage interventions for the population.

The fact that they are also intended for children for the most part, furthermore introduces an important factor of equity, since it allows the protection of a category of vulnerable subjects. Moreover, the immunisation programmes come under parental responsibility according to the criterion of the highest interest of the child and his/her right to be vaccinated. The consequence of any type of refusal is that the risk of frequenting many places increases for the children (hospital, school, gyms, swimming-pools, public and private playgrounds, etc.) which become risky by very reason of this refusal. Above all, vulnerable subjects who cannot be vaccinated for health reasons are put in serious jeopardy.

Furthermore, it must be underlined that, at the basis of the decision to be vaccinated, as well as the protective effect of immunisations (the so-called *herd immunity*) and the reasons connected to this of a solidarist and cooperative nature, must be added further reasons regarding personal interest; in the absence of a proper immunisation diffusion, the individual risk of falling ill is greatly superior to the risks linked to the vaccination itself. It must not be forgotten in fact that the eradication of an infectious disease cannot be guaranteed exclusively by other hygiene-healthcare measures, as shown by the re-emergence of recent epidemics in the industrialised countries too.

To this aim the ICB recommends:

- Advertising and informative campaigns on mandatory and recommended vaccinations at the national level, to be implemented without delay and based on consolidated scientific documentation, including efficient communication on internet sites and detailed written and oral information at the individual level, so as to make citizens aware of the ongoing strategies and the benefits in relation to the possible risks.

- Information and awareness campaigns for healthcare centres, family doctors, family pediatricians and the professionals involved in immunisation programmes, as well as school employees.

- The commitment on the part of the healthcare institutions to organise specialised centres specifically dedicated to the immunisation of subjects that are most at risk.

- The analysis of the regional area so as to introduce more efficient organisation modalities, also with the main objective of overcoming the differences existing today in the different Italian regions in the respect of constitutional principles.

- The respect of the mandatoriness of an adequate prophylactic immunisation for healthcare professionals and the personnel working in schools of all levels – and in general in places most frequented by children – according to their specific activity.

- The commitment – particularly by family doctors and attending pediatricians – to give sufficient information regarding their patients, highlighting how vaccinations constitute one of the most efficient treatments, with a very positive risk/benefit ratio.

- The continuous monitoring of non-immunisation (due to forgetfulness or for medical, ideological, religious, psychological reasons etc.) both at the national and single municipality level with the aim of identifying those who need to be encouraged to do vaccinations (*compliance*) and stressing any immunisation coverage deficiencies, especially in children.

- The classification of "healthcare and public hygiene emergencies" in such a manner as to be able to study and draw up *healthcare emergency recovery plans* to be sanctioned and set up when needed case by case.

- The setting up of repeated actions and adoption of emergency measures In urgent situations and - possibly legislative interventions – needed to restore or achieve an acceptable level of health safety which can be obtained by keeping immunisation coverage high.

In conclusion, the Committee considers that every possible effort must be made to achieve and maintain an optimum immunisation coverage

through education programmes for the public and the healthcare professionals, not excluding the possibility of making them compulsory in emergency cases.

** ** **

The text of the motion was voted on and unanimously approved by those present in the plenary sitting: Profs. Salvatore Amato, Luisella Battaglia, Bruno Dallapiccola, Antonio Da Re, Lorenzo d'Avack, Mario De Curtis, Riccardo Di Segni, Carlo Flamigni, Paola Frati, Silvio Garattini, Assunta Morresi, Demetrio Neri, Andrea Nicolussi, Laura Palazzani, Rodolfo Proietti, Massimo Sargiacomo, Monica Toraldo di Francia, Grazia Zuffa.

The members without the right to vote expressed their approval: Dr. Carla Bernasconi, Dr. Rosaria Conte, Prof. Anna Teresa Palamara, Dr. Carlo Petrini.

Profs. Carlo Caltagirone, Stefano Canestrari, Cinzia Caporale, Carlo Casonato, Francesco D'Agostino, Marianna Gensabella, Giancarlo Umani Ronchi, Lucetta Scaraffia were absent in the plenary session but endorsed the opinion at a later date.

Presidenza del Consiglio dei Ministri



MOBILE HEALTH APPS: BIOETHICAL ASPECTS

28 May 2015

Overview

The phenomenon of "mobile-health" or the collection of "mobile" technologies, wireless communications (phones and smartphones, tablets, digital devices, with or without wearable sensors), applied in areas related to health arises within the context of the "mobile revolution" and transformation of new information and communication technologies.

The development of such technologies is fast and constantly growing, inasmuch as it is difficult to offer a concise overview of the new technologies available. These are technologies that promote strong innovation and open up new opportunities: including, the promotion of a healthy life style of its users, facilitation of communication between doctor/patient, improved efficiency of the health care system, the speeding up of the collection of data, the expansion of access to care, etc..

At the same time there are some controversial aspects involved and discussed in ethical terms, with respect to safety and efficacy, privacy, informed consent, technological dependency and vulnerability, health self-management and the technological divide.

In the light of the ethical analysis the Committee has made some recommendations, by placing particular emphasis on the classification of the applications based on the risks, the promotion of interdisciplinary research between computer experts, programmers and doctors, along with ethicists, and experts in cognitive and social sciences, during the stages of development, testing and evaluation of applications, encouraging industries to create apps which are actually useful for the health of citizens and identifying company responsibilities in building apps as part of the profiles of safety and privacy.

The Committee calls for the establishment of an observatory to monitor apps and the setting up of scientifically accredited sites and/or portals, the promotion of an appropriate information sheet and clear communication for the user whenever using the app, paying specific attention to minors and fostering studies on the impact of the use of apps, particularly in regards to personal identity and relationships. The goal is to promote the acquisition of a critical awareness on the part of society of new health applications, avoiding excessive forms of health fanaticism and medicalization. A concise overview of the current major international and national regulations is appended to the document.

The text was written by Professor Laura Palazzani who benefited from the critical notes and written contributions by Profs. Lorenzo d'Avack, Salvatore Amato, Silvio Garattini, Demetrio Neri, Carlo Petrini. The text also took into account the remarks and additions made by Professor Roberta Siliquini, professor of public health at the University of Turin and President of the Superior Council of Health.

During the discussions on the topic the ICB invited for auditions Prof. Claudio Conti, Director of the Institute of Complex Systems of the CNR; Dr. Allen Francis Farrelly, CNR researcher and developer of health applications; Prof. Riccardo Pietrabissa, member of the General Scientific Council of the CNR, Acting Director of the ICT Department of the CNR, Full Professor of Industrial bioengineering at the Polytechnic University of Milan.

The document was unanimously approved at the plenary session on 29 May 2015 by those present: Profs. Luisella Battaglia, Stefano Canestrari, Carlo Casonato, Francesco D'Agostino, Antonio Da Re, Lorenzo d'Avack, Mario De Curtis, Carlo Flamigni, Marianna Gensabella, Assunta Morresi, Demetrio Neri, Andrea Nicolussi, Laura Palazzani, Massimo Sargiacomo, Lucetta Scaraffia, Monica Toraldo Di Francia, Grazia Zuffa. The advisory members: Dr. Maurizio Benato, Carla Bernasconi, Carlo Petrini also espressed their endorsement to the document.

The Opinion was later endorsed by the following members of the Committee, absent during the plenary meeting: Profs. Salvatore Amato, Carlo Caltagirone, Cinzia Caporale, Rosaria Conte, Bruno Dallapiccola, Riccardo Di Segni, Paola Frati, Silvio Garattini, Anna Teresa Palamara, Rodolfo Proietti, Giancarlo Umani Ronchi.

1. Definition

The term "mobile-health" or "m-health" generally means the collection of "mobile" technologies, i.e. the use of wireless communication (phones and smartphones, tablets, digital devices, with or without wearable sensors), applied in the medical-healthcare field or in related fields of health[88].

There is talk of "mobile revolution" as a pervasive phenomenon in the society we live in, even in the healthcare sector: information is transmitted to anyone, it is received, and stored everywhere, at any time, with any device. Ubiquity, globality, and instantaneity constitute intrinsic elements in the digitalized networked society.

2. Diffusion of the phenomenon and context of development

A recent study in 2013[89] noted that on the market there are about 97,000 apps, distributed on different platforms; about 70% of these are related to the health and well-being of the consumer, while 30% is dedicated to consultation and monitoring of the patient, diagnostic imaging, pharmaceutical information etc..

Some statistics[90] foresee that in 2016 there will be 3 million patients monitored with such technology and that by 2017 about 3.4 billion people worldwide will have smartphones using applications for health. It is estimated that in 2018 there will be 1.7 billion users worldwide. We are moving from Internet 2.0, the Internet of communication through the proliferation of social networks, to Internet 3.0, the *so what* Internet, "something" that will form an integral part of our life, "something which we can-not do without"[91]. In this step the body and, by reflex, health will be subject to a multitude of potential points of observation and monitoring of movements, sounds, lights, electric potential, temperature, humidity, location, voice, face, heart rate, changes of thermal and electric energy of the skin, volume

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[88] mHealth Summit FNIH, *The delivery of healthcare services via mobile communication devices*, 2010. Applies to both software and hardware, "Healthcare delivered wirelessly".

[89] Research2Guidance, *The mobile health global market report 2013-2017: the commercialisation of mHealth apps"*, 2013, Vol. 3.

[90] *Ibid.*

[91] For a comprehensive view of the phenomenon see WHO, *mHealth: New horizons for health through mobile technologies*, Report 2011.

of blood flow, the contraction of muscles[92]. There are at least 100,000 applications available on the market in the category "Health & Fitness", with a steady growth over the years.

The transformative potential of this new technology in a growing market has and will always have greater implications on different levels, with a rapid pace of evolution we can now only imagine the economic and organizational developments (for the provision of services) and on a cultural level, the international and national effects.

On the one hand, the likely increase in health care costs both due to the increase in the elderly population and chronic, multifactorial diseases and to the personalization of health (the so-called *precision medicine*) which demands and will increasingly require the use of technologically innovative organizational models, in order to redesign services, multi-professional and multidisciplinary interventions, at different times and places. On the other hand there is talk about increasing the active participation of citizens, ever more willing to manage their own health and well-being and to seek, through information and communications technology (ICT), service excellence.

M-health fits into this context of technological evolution - the transition from substitution technology to control technology - and the transformation of health, giving rise to increased accessibility (even economically), efficiency of services and a growing involvement of the subject/user, who by using mobile devices or sensors for the collection of clinical data plays an increasingly important role in his/her own health. Firstly, as a matter of fact, the user is active in the search for relevant information about his/her health. Secondly, the user is a source of valuable data, contributing to fuelling the pool of information on which to draw from in order to respond to his/her personal queries. As is typical of Web 2.0, the user is a *prosumer,* producer-consumer of resources, and in this case, of information.

3. Some preliminary remarks

The development of such technologies is rapid and constantly growing, inasmuch as it is difficult to provide an overview and understanding of the

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[92] M. SWAN, *Sensor Mania! The Internet of Things, Wearable Computing, Objective Metrics, and the Quantified Self 2.0,* "Journal of Sensor and Actuator Networks", 2012, 1, p. 219.

new technologies available; any attempt to do so would be doomed to grow old quickly, given the speed and dynamism of innovation in this field. It is useful at the outset, to introduce some preliminary remarks in terms of technologies applied to health, their purposes, and the subjects involved.

Regarding technology we need to distinguish:
- mobile platforms which, while not emerging from a medical context, turn into medical devices or extension of medical devices that collect, analyze, transmit data or images relating to health[93].
- Accessories (video-cameras, microphones, sensors[94], physiological parameter detectors) providing support or assistance to devices.

b) Regarding health-related[95] purposes a distinction must be made:
- Applications for well-being (wellness-fitness): counting calories, steps and movement, monitoring of emotional state, etc.[96].
- medical applications for health in the framework of prevention (devices to record physiological functions such as heartbeat, breathing, pressure, temperature, brain activity etc.)[97], diagnosis (e.g. diagnosis of melanoma), in the treatment of diseases (e.g. medical remainder to improve adhesion to treatment, calculating the dosage of the medication, monitoring of metabolic diseases), for assistance (e.g. care for the disabled with limited mobility).

c) Regarding the subjects potentially involved: citizens/patients, doctors, health facilities, in some respects closely related to well-being, physical therapists and personal trainers, providers, app manufacturers or developers or designers (sellers; pharmaceutical industries).

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[93] If the software has a medical purpose (diagnostically or therapeutically) and is used in a smartphone - which is not a medical device - the question arises as to which software can be a medical device. Sofware in itself (stand alone software) can be a medical device, if it has medical functions.

[94] E.g. bracelets, watches.

[95] There are also non-medical applications, e.g. administrative procedures such as booking tours, remembering appointments, managing resources.

[96] Examples of such applications are: `iFood` as a daily agenda for nutrition, 'caffeine areas' for the measurement of caffeine ingested, etc.. F. BERT, M. GIACOMETTI, M. R. GUALANO, R. SILIQUINI, *Smartphones and health promotion: a review of the evidence,* "J. Med Syst.", January 2014, 38 (1): p. 9995; M. GIACOMETTI, M.R. GUALANO, F. BERT, R. SILIQUINI, *Public health accessible to all: use of smartphones in the context of healthcare in Italy*, "Ig. Sanita Publ." March-April 2013, 69 (2), pp. 249-59.

[97] Examples of medical applications for health: 'Welp' to detect the paralysis often characterizing seizures; applications for preventing falling of elder people; applications to identify the first signs of Parkinson's disease; applications to manage certain diseases (HIV, diabetes, chronic conditions).

4. New opportunities for health

The Committee believes that these are technologies and innovations with enormous potential for the improvement of public and personal health. Among the positive factors of these new technologies, already present in our society, we will briefly recall some aspects:

a) promotion of a healthy lifestyle: improving awareness, active participation and motivation of individuals as concerns health
b) facilitation and speeding up of doctor/patient communication, personalization of treatments, increased autonomy and safety of the patient who can be controlled and localized at a distance
c) improving the efficiency of the healthcare system: reduction of costs for care and hospitalization, analysis by the use of remote monitoring and telemedicine, speeding up and enhancing communication of information to the patient by the healthcare facility
d) the contribution to research: facilitating individual and environmental data collection, useful for the individual as well as the community (especially epidemiological research, the study of the correlation between certain medical and environmental conditions, etc.)
e) expansion of access to treatment, with the ability to reach users who would otherwise not have medical care
f) stimulating the transfer of research, to production and to innovation, even through the creation of dedicated start-up companies
g) the potential also for the possibility of sharing clinical cases and requesting a second opinion in real-time for physicians.

5. Elements of ethical problematicity

Given these positive data of great interest for scientific and technological progress, the Committee believes, however, that the ethical problematicity of some emerging aspects should be highlighted[98]. It is important to reflect on these elements, certainly not with the aim of curbing this field of

[98] It is a bioethical topic connected, in some ways, to issues previously dealt with by the ICB. See: *Ethics, health and new information technologies,* April 21, 2006*; The identification of the human body: bioethical aspects of biometrics,* November 26, 2010.

technological development, but rather to make it compatible with the protection of the rights, safety and well-being of users.

5.1. Safety and efficacy

The fundamental ethical aspect regards the protection of health of the user or safety.

A first essential element is the determination of criteria for the distinction of m-health applications that come under medical devices and the applications which do not come under medical devices.

According to the Italian legislation, a medical device "means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: diagnosis, prevention, monitoring, treatment or alleviation of disease; diagnosis, monitoring, treatment, alleviation or compensation for an injury or handicap; investigation, replacement or modification of the anatomy or of a physiological process; control of conception, which does not achieve its principal action in or on the human body that is targeted by pharmacological, immunological or metabolic means but whose function may be assisted by such means".

This distinction is important because in the first case the applications on health, before being allowed on the market, must comply with European regulations and certification requirements: the rules governing how the devices should be used, by whom, and which their applications are; certification guarantees safety, meaning not being dangerous, but it does not refer to efficacy. In the second case - that is, when the applications for health are excluded as medical devices - there is no specific regulation, but only the general protection of the consumer.

The Community Directives[99] regulating uniformly in all the countries of the European Union the medical device industry delegated to the Competent Authority (CA) in each Member State the designation of Notified Bod-

[99] See Directive 93/42/EEC on medical devices, Directive 98/79/EC in vitro diagnostic medical devices, Directive 90/385/EEC on active implantable medical device. See Appendix.

ies, which evaluate, monitor and verify medical devices. The Notified Body, in fact, is a public or private entity authorized by the Competent Authorities to issue the CE marking.

Reference is made to the risk level of the device, according to a precise classification: class I (low risk, e.g. corrective glasses); class IIa (e.g. contact lenses); class IIb (medium to high risk, e.g. X-ray machines); class III (high risk, e.g. coronary stents); active implantable devices whose risk is equated to the class III (e.g. pacemakers). When at high risk (because, e.g., it comes into contact with the cardiovascular or neurological system) the evaluation is entrusted to the Notified Body; when at low risk it is the actual manufacturer that identifies the presence/absence of the requirements for classification. This is probably the reason why there has been a greater diffusion on the market towards more applications that fall into the category of wellness and fitness, not classified as medical devices.

What becomes manifest today is that there is an extremely efficient system of control by the operators of the store or online sales office of health apps. However, these operators are not scientific bodies and are interested in entering the health market, but not to sell "medical devices" that would require the "developer" to accept rules and very strict conditions within the territory in which they are produced and are intended to be distributed. A lengthy, burdensome and expensive procedure, with repercussions related to legal liability. There is a tendency, therefore, to circumvent this by presenting as a simple method for verifying well-being what in actual fact is a genuine medical device. Therefore, there is an ambiguity in the supply of health applications. On the one hand, Google and Apple keep their "distance" from medical applications in the strict sense, on the other hand they are "close" to health, placing on the market applications which, while not being classified as medical, are increasingly numerous and always more related to medicine.

As part of the dissemination of information and communication technologies, what tends to prevail in the market for health apps is the opinion of people who have downloaded and tried them, instead of expert assessment. This is the criteria of evaluation in this area, in which everything changes very rapidly; what has a real impact is what the users see as being reliable, judging from the number of downloads and the views expressed on the network. In this sense what drives users to install an app is not so much

scientific validation rather than the approval ranging on the network expressed by consumers.

What often emerges is the absence or deficiency of adequate scientific validation of the applications with regards to safety and efficacy.

While the testing of medical devices is subject to very precise regulation, there is no regulatory requirement for testing apps not classified as devices, but it is ethically desirable that the developers at the time of proposing a prototype, submit it to validation or evaluation of the risks and benefits. Considering that the general information related to health and well-being must be accurate and reliable, because critical decisions regarding the health of the subject may be based on it.

Certain studies have shown that there are few applications for health and well-being that have been adequately tested[100]. Some applications on the market can jeopardize the health of the patient and are potentially dangerous for clinical use. Especially, e.g., some apps for the dosage of opioids, the prediction of cardio-vascular risk or the diagnosis of melanoma have proved to be inaccurate[101].

In this regard - given the lack of adequate testing - it may be necessary to check the variables that can affect risk in the use of apps, distinguishing the internal risks of the apps (e.g. the display) and external risks (the context of use). Internal risks could be reduced with proper regulation; external and contextual risks through suitably educating doctors (if the use is clinical) and/or the users, to make them aware of proper use.

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[100] G. EYSENBACH, *mHealth and Mobile Medical Apps: a Framework to assess risk and promote safer use,* "Journal of Medical Internet Research", September 2014, 16 (9), e210; S. MISRA, T. L. LEWIS, T. D. AUNGST, *Medical application use and the need for further research and assessment in clinical practice: creation and integration of standards for best practice to alleviate poor application design*, "JAMA Dermatol.", June 2013, 149 (6), pp. 661-662.

[101] On these issues, there is already a wide-ranging debate: M. MCCARTNEY, *How do we know whether medical apps work?*, "BMJ", 2013, 346, p. 181; A. W. BUIJINK, B. J. VISSER, L. MARSHALL, *Medical apps for smartphones: lack of evidence undermines quality and safety,* "Evid. Based Med. ", June 2013, 18 (3), pp. 90-92; F. HAFFEY, R. R. BRADY, S. MAXWELL, *A comparison of the reliability of smartphone apps for opioid conversion,* "Drug Saf", in February 2013, 36 (2), pp. 111-117; J. A. WOLF, J. F. MOREAU, O. AKILOV, T. PATTON, J. C. INGLESE, J. HO, L. K. FERRIS, *Diagnostic inaccuracy of smartphone applications for melanoma detection, "*JAMA Dermatol", April 2013, 149 (4), pp. 422-426. The problem that remains open on the practical level concerns the fact that the exponential rate of designing new apps, makes it difficult to carry out the evaluation of the risk/benefit. Medical apps are not designed to function in a particular device, but can work with different operating system. Given the versatility of operating systems (current and future), it is not possible to test them all for safety.

However it has been shown that some health related applications with clinical use do not provide training for doctors using them and that they do not involve doctors in the design and development process[102]. Often the designer has great technological knowledge, but a lack of medical expertise; the doctor, in turn, is familiar with the scope of application, but knows little about technology; the user, ultimately, tends to rely on technology, often without being adequately informed about the limits of safety and the possible risks.

5.2. Use of data and privacy

The considerable amount of data collected and analyzed by users (health and medical, personal, biometric, social and environmental data) and the ubiquity and continuity of the process of communication in the so-called *mobile ecosystem* (including providers, manufacturers, vendors and users) raise many relevant issues regarding privacy[103].

It generates a huge amount of complex, heterogeneous data, rapidly and continuously accumulated through the monitoring of physiological parameters that are collected, studied, interpreted and correlated with algorithmic models. This explosion of information raises some controversial aspects regarding privacy in relation to their use by parties unrelated to the therapeutic relationship or for non-therapeutic purposes.

The problem of the *third party request* is becoming even more crucial within the use of the network. As the ICB has emphasized in the document The identification of the human body: bioethical aspects of biometrics, any information may be relevant and become discriminatory when connected to others and used to make "profiles" of individual users. The collection of data relating to health, or even just regarding requests for healthcare information, may give rise to elements of relevance for the market of pharmaceu-

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[102] E.g. some applications for asthma, food diary for diabetics, my recovery applied to preparation management for operations and after surgery, for rehabilitation; use of games to control panic attacks; home HIV testing, sexual diseases, streptococcus.

[103] As part of the processing of sensitive data: Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data; Directive 2002/58/EC concerning the processing of personal data and the protection of privacy in the electronic communications sector. See Appendix.

ticals, medical services, insurance and labour. Without appropriate regulation and a rigid system of restrictions and controls (such as through the clear separation between search engines and search sites) it is difficult to prevent from occurring - in some areas - serious phenomena of marginalization and discrimination, linked to the profiling system (how is it possible to prevent, for example, those visiting sites or purchasing apps for heart problems, from being classified as possible cardiopaths and subsequently prevent this information from reaching the labour market or the insurance market?). These phenomena become even more serious in so far as they occur without the person's knowledge and may call for forms of protection or the defense of one's rights.

The problem not only affects health and medical data, but also data obtained from apps for wellness and lifestyles. This data is called "raw" (raw data) even if they are not directly medical, combined with other data, they may have a medical importance and allow for the definition of a health profile of the user, with reference to health and to the risks for health[104]. Caution should be taken because, despite being health data, they are currently treated as personal information, therefore with a lower level of protection[105].

What also emerges is the concern that the use of apps leads to maximizing the use of medical/personal data without any appropriate knowledge, or rather with indifference or even for recreational purposes, especially among young people.

Therefore, the following problematical elements related to privacy need to be pointed out:

a) a lack of transparent information to users, before downloading the application of data, on what and how much data is used for possible research (for scientific, epidemiological or commercial purposes, or in any case used for purposes that are not necessarily in the interest of subject); who the data is used and managed by (*data controllers*); where the data is

[104] E.g. if one collects data of the counting of number of steps taken once only, such data reasonably will not lead to any inference. These are not data in a medical context and are not correlated with other data, therefore not relevant for research. But if they are systematically collected and combined with other data (e.g. gender difference, age, habits) they can become important for research.

[105] See, as noted, art. 29 Working Party, see Appendix.

stored (*data repository*); a lack of information as to whether the data is to be combined with other data from which health-related information can "reasonably" be inferable;

b) absence of information on the possibility of withdrawal of consent, rectification and destruction/erasure of data;

c) the absence of information on the risk of identification, when partial anonymization is not possible or guaranteed;[106]

d) a lack of information on the risks of data access by third parties (insurance companies, employers, etc.) and the possibility that those who store data may 'sell' it to form research databases (commercial/scientific). In some cases, it is stated that data will be used for commercial purposes, but often in special sections of the app this is not readily available for those who do not have adequate computer skills. In some others this information is relegated to third party websites and therefore is not present within the app.

An interesting aspect that is emerging in the ethical debate is that the very construction of applications is based on the requirement of *privacy by design* as a condition of the same legitimacy of the app. It is an expression that indicates the possibility that the issue of privacy is already considered at the design stage of the application, for example through the construction of applications that have *a priori* determined the manner and limits of access to personal data, the possibility of control over who has access, from manufacturers and users, the request only for the data required for the app functioning, the effective revocation of data on demand[107].

5.3. Informed consent

From the above, the ICB, although it is well aware of the difficulty of realizing informed consent and protecting the privacy of users in this new field of application, nevertheless, it hopes there will be the possibility of

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[106] There may be used authentication systems based on biometrics, tokens, technical log tracking, similar to the banking sector (*digipass, SMS authentication*).

[107] Art. 17 Directive 95/46/EU, art. 14.3 Directive 1999/5/EC and art. 23 of the Proposal for the Regulation on data protection: "the controller shall implement appropriate technical and organizational measures and procedures in such a way that the processing will (…) ensure the protection of the rights of the data subject").

giving appropriate information and a transparent communication at the time of using the app so as for achieving informed consent.

However, how should the patient be informed about the related security and privacy issues?

The Warsaw Declaration on the *appification of society* (September, 2013), in the context of the meeting of the Data Protection and Privacy Commissioners, 35th annual international conference, proposed the so-called "granular consent"[108] indicating that the consent must be given for each type of information. The subject should therefore express different consent: general consent to download the app and a separate consent for the specific purpose of the app. Each type of consent should be preceded by separate information[109].

This solution has several problematic elements. Firstly, there is so much digital information written in small characters to display on smartphones; sometimes the real alternative of dissent or change of choice is absent. There has already been concern that the informed consent displayed on screen and not on paper, leads to clicking in an immediate way without sufficient time for making an informed choice and without the possibility of ascertaining actual voluntariness. Furthermore, the multiplication of consent may lead to the annoyance of the user or often to giving consent just in order to speed up the procedure, without - here as well - adequate awareness. In this way, the meaning of informed consent would be undermined[110].

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[108] See par. 6: "individuals can finely (specifically) control which personal data processing functions are offered by the app they want to activate".

[109] This is the line of thought based on the interpretation of par. 107 of the "Explanatory Memorandum" of *Recommendation N° (97) 5 on the protection of medical data*: "But even in cases where his/her consent is not required - that is, when the collection and processing of medical data follow an obligation under the law or under a contract, are provided for or authorised by law, or when the consent requirement is dispensed with - the recommendation provides that the data subject is entitled to relevant information". Also art. 29 Working Party has recently published a document "*On apps on smart devices*", which emphasizes the need to inform in a clear and unambiguous way the way in which the data is used (data type, purpose, period) before installation of the app. The right to be informed is also expressed in art. 10 Directive 95/46/EC; art. 5.3 of the ePrivacy Directive 2002/58/EC.

[110] E. MANTOVANI, P. QUINN, B. GUIHEN, A. HABBIG, P. HERT, *eHealth to mHealth – A Journey Precariously Dependent Upon Apps?*, "European Journal of ePractice", November 2013, vol. 20; M. PARKER, *Ethical considerations related to mobile technology use in medical research*, "Journal of Mobile Technology in Medicine", 2012, 1, 3, pp. 50-52; M. J. SIÒLBERMAN, L. CLARK, *M-Health: the union of technology and healthcare regulations*, Greenbranch publishing, 2012.

This need to inform users and receive their consent becomes even more complex when the apps are used by children, as occurs with great frequency, both medical and non-medical apps. So, what are the precautions to consider before a teenager or older minor downloads a health app?

Obtaining informed consent in the medical field presupposes symmetrical and reciprocal communication. Communication is symmetrical when individuals are equally powerful in the interaction and it is reciprocal when the positions between those giving the information and those receiving the information take place in the recognition of their respective autonomy. If this already appears hardly feasible to ensure with regard to an adult in the use of medical apps, where the relational context is missing, it is even less so for teenagers whose elements of competency, such as the ability to decide, the reasoning of decisions, the prediction of outcomes, involve a balance between these elements that is established only progressively during the stages of development.

One must also consider that it is legally debatable that such consent could nevertheless be given merely by the child; since these matters concern the child's health, they must necessarily fall under the responsibility of the parents or legal representative. Moreover, if the risks associated with these medical devices are consciously undertaken by an adult, the same can-not apply for a minor, as his best interests in the context of care is still represented by traditional use of the patient-doctor relationship. Particularly, since the most downloaded apps by users, as mentioned above, request access to a large amount of data, without even adequately explaining the purposes for which this information would be used, the possible personal data that will be collected and the purpose of this.

However, it is difficult to know whether the use of the medical app is carried out by an adult or a minor. This is a problem that, even in the field of ICT, should be highlighted: thought should be given to providing specific additional guarantees for minors, by identifying, for example, information technology requirements and mechanisms to verify the age of the purchaser of an online health application. It also follows that there is a need to provide, precisely for minors, simple, and concise information that also includes educational references which encourage awareness of the issues, using suitable language. The education of minors, active users of these new technologies, is particularly urgent and relevant in terms of bioethics: an education en-

hancing the instruments of self-defense of young people in the context of the use of technology. It should also be on the part of the parents, that are the buyers of mobile technologies for their children, to make use of control systems (*parental control*) for accessing the app which should be included in the system by the manufacturer.

Furthermore, it is also auspicable that the medical app, which contains data and treatments aimed at minors, should be designed, supported and endorsed by scientific companies or health institutions specialized in diagnosis and pediatric care. The same proposal on the market should be diversified in relation to target recipients (adults or minors).

5.4. Dependency and technological vulnerability

A simple *touch,* just one "touch", is all that is needed to enter the world of infinite potential that mobile-health offers to health protection and the construction of individual identity via continuous comparison with one's own body, even in its most hidden and blurred aspects, such as change in blood glucose levels or cardiac arrhythmia. Is one "touch" sufficient even to pull through? At what stage does an increasingly pervasive supply of medical and therapeutic indications end up becoming obsessive, deeply affecting an individual's existence and patterns of coexistence?

As already pointed out, various forms of addiction both individual as well as social and political, may develop.

"Personal dependency" is expressed through attention to the single changes in one's physical and psychological condition, which could lead to a genuine health consciousness pathology, exacerbating the fear of disease and morbid attention to the most insignificant details and consequent medicalization, the phenomenon of the so-called "quantified self"[111]. This expression indicates a tendency to incorporate technology in everyday life with the recording and comparison of real-time data on human activity: measurement of food consumed, number of kilometers covered, control of the calories consumed, the quality of the air breathed,

[111] *Quantified self* is a movement of thought that was born in the scientific field (in San Francisco in 2007) and has become a "philosophy of life", summed up in the slogan "I quantify, therefore I am". On the topic see *Le corps, Nouvel Objet Connecté, du Quantified Self a la m-Santé, les Nouveaux Territoires de la Mise en Données du Monde*, Commission National de l'Informatique et des Libertés, May 2014.

registration or the emotional state of physical and mental performance[112].

This trend is part of a wider context in which prevention is increasingly understood in an individualistic sense, devaluing the collective dimension of health, the importance of which is specifically mentioned in our Constitution; it results in the induction of specific lifestyles, in emphasis on control, self-management of health and individual responsibility for one's own health. A similar trend may contribute to exacerbate forms of health fanaticism and the medicalization of life, as well as even the capillary government of people's lives, putting a particular emphasis on health reductively understood as only physical well-being.

One might also configure a "social dependency" with the creation of "norms of behaviour" that help to continuously redefine and elevate the standard "performance" regarded as "normal" in society, which ends up imposing itself on others, in a race to health fanaticism as well as consumerism (market pressures to buy new apps or supplements or drugs to improve physical and mental performances), medicalization (considering inability to achieve certain objectives, as an illness which creates discomfort)[113]. A condition that can lead to the expropriation of one's autonomy by the market, but even by oneself. Those who do not use these technologies could be regarded with suspicion and suffer serious limitations in relational life.

One could envisage even scenarios of "political dependency"; the utilization of these technologies could become mandatory, reducing the space for individual autonomy and justifying an increasingly intense intrusion in one's personal sphere. Let us take the possibility that in the near future citizens wanting to take out life insurance and/or health insurance policies could be classified in different `*clusters*` and be granted more favourable

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[112] This phenomenon has been interpreted as the application of the scientific method to the personal sphere, with the aim of biometrically quantifying oneself and data sharing through ICT. The urge to quantify oneself and to "datify" one's corporeal and psychical functions can arise from the desire of self-control; by measuring one feels able to exercise power over themselves. Keeping tabs on what you can do gives the feeling of being masters of one's own destiny in an era like ours, marked by uncertainty. The difficulty or impossibility to control the world and what is happening around us urges to fill with a sort of "compensatory mechanism" such a lack with the will to control what becomes technologically controllable.

[113] The issue was addressed by the ICB in the opinion *Neuroscience and pharmacological cognitive enhancement: bioethical aspects*, March 13, 2013.

economic conditions, depending on the proven use of such technology packages, with the result that its use would be made "almost obligatory" otherwise the penalty would be exclusion from the groups of policyholders with a lower premium.

It could then give rise, if not already underway, to a form of "economic dependency" so that the price of these technologies, at first negligible, will tend to increase insofar as the demand increases along with their widespread and systematic use. We cannot forget that it is primarily the market that stimulates and fuels the proliferation of mobile-health and therefore it will be the market, without appropriate regulation, to decide on prices and terms of use. As mentioned, the offer of free access to certain benefits in exchange for the waiver of confidentiality in data processing is ever more frequent. What and how many other constraints could emerge in time and with use?

Dependency is not a new phenomenon. In many respects our whole existence is built on the needs, desires and passions that make us "dependent" from others and from things. In mobile-health, this phenomenon occurs in a variety of ways, exacerbating that impelling urge for attention and reputation that so belongs to social networks, through the fear of illness or the obsession with health. It should not be ruled out that the ease of access, utilization in solitude, compulsiveness waiting for the results may develop pathologies similar to those already found in compulsive gambling.

Alongside regulations and controls there is, therefore, the more general problem of training to use this means of gaining information and relating with one's own body and health. The existence of increasingly complex and refined technology without a corresponding rise in the level of awareness and culture is inconceivable.

5.5. *Health self-management*

Is Google now the first doctor for Americans? Will it be even more so with the Apple Watch on the market, the watch designed to ensure the continuous monitoring of our health interconnected with all services offered by the Internet?

New technologies can play a decisive role to fundamentally change the way in which citizens manage their own well-being and health. There is the phenomenon of more active participation by the individual due to improvement in education levels (in technologically advanced countries) and the in-

creasingly pervading availability of ICT as an instrument of knowledge, within the context of changes of a cultural nature that tend to reduce the constitutive asymmetry of information between doctor and patient.

The active participation by citizens in the management of their own health is extremely positive, but it can have negative implications insofar as it is expressed as a desire for self-medication: the citizen/patient may feel able to take care of oneself and be responsible for one's own health, without feeling any need for a doctor. The ability to download independently from the internet *ITest/home-testing* and IT tools that enable analysis, interpretation and visualization through diagrams with comparative data at any time and place, can lead to self-medication, self-diagnosis, and self treatment[114].

In some respects, this can have advantages in the prevention of disease and the maintenance of appropriate lifestyles[115].

The ethical problem emerges in relation to diagnosis and treatment of pathologies, when the patient does not have sufficient skills and information to make a direct medical assessment by himself. There is, in this context, the problem of medical expertise and computer/digital ability for the safe use of the technical tools available, as well as the reliability/security of the same technologies. The user can have access to data that were once generally mediated by a doctor, while today these may be obtained directly.

In this sense, applications for medical purposes (diagnosis, treatment, care) should require for medical supervision (information at the moment of downloading the app/conditions for downloading the app). It should be the doctor to adequately inform the patient and to make sure the patient is able to use such an instrument, and that it is reliable, to avoid forms of self-management by the patient that would endanger his health.

Even on the part of the doctor the use of m-health can have many advantages, enabling real-time monitoring of the patient at a distance, it is an improvement in care in terms of quantity and quality. At the same time it

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[114] The possibility of purchasing drugs and substances online, even dangerous ones, such as opioids, by users without any prescription from the doctor, has to be emphasized. See in this regard: F. BERT, V. GALIS, S. PASSI, MR. GUALANO, R. SILIQUINI, *Differences existing between USA and Europe in opioids purchase on Internet: an interpretative review*, "Journal of Substance Use", 2014, Early online: pp. 1-8.

[115] See ICB, *Lifestyles and Health Protection,* March 20, 2014.

can become a form of removal of responsibility from the doctor, and "passing" it to the patient, by increasingly restricting face-to-face appointments and thereby reducing the interpersonal relationship (replaced with video-appointments) impoverishing or even eliminating the relationship with the patient.

5.6 The digital divide

The problematicity detected in the use of technology should not however overshadow its unquestionable importance and the opportunities acquired by our society (cf. § 4).

Insofar as the undoubted advantages of appropriately-used m-health are recognized, the problem of exclusion of those without access to technology emerges, namely the problem of the gap between those who have the tools and skills and those who are marginalized due to a lack of technology or lack of knowledge of the use of technology and/or stimulus for knowledge.

In this sense, it is essential to reflect upon a fair distribution of technology resources, on the extension of the right of access to new technologies for all, including disadvantaged and vulnerable groups (the elderly, the disabled, the indigent and those not sufficiently competent to actually use technology).

An essential element is to appropriately educate citizens to use the new technologies for mobile-health, in order to obtain adequate skills for properly using such tools. Non-discrimination should also be guaranteed towards those who cannot or will not be able to access these medical technologies, by ensuring the provision of alternative solutions for health treatment.

This problem is known as the *digital divide* which can certainly have among its causes the lack of computer skills and deficiencies in the capacity of interpretation of the information available via the app. However, it should be recalled that this gap can be associated with other reasons such as the cost of mobile devices (smartphones and tablets) therefore a socio-economic gap and the network coverage for the Internet in the area under consideration. These variables can strongly influence equity of access to possible healthcare services offered through m-health.

6. Recommendations

The Committee recognizes the importance, the positiveness and the great scientific relevance of technological progress in this area. While recognizing this importance, given the issues related to health and privacy that are nevertheless present, it highlights certain ethical recommendations. The Committee recommends:

- drawing up of internationally agreed criteria for classifying software used as medical devices, distinguishing them from those that are not medical devices, specifically differentiating the applications for health in the proper sense and the applications for wellness /fitness;
- promoting interdisciplinary research between computer experts, engineers doctors, together with ethicists, cognitive and social sciences experts, in the phase of design, testing and evaluation of the applications as to ensure the protection of health, privacy, and autonomy;
- encouraging developers and industries to produce apps which are actually useful and reliable for the health of citizens;
- identifying the responsibility of companies/industries that produce apps, placing as requirements to design the safety and minimization of data collection - as far as possible - making data anonymous;
- establishing an observatory to monitor health apps in order to devise potential risks and the possible need to revise regulations; it is hoped that scientifically accredited sites and/or portals will be established with guidance on the classification of health applications on the market, continuously updated (at least for the most popular apps), in relation to the risks;
- promoting an appropriate information sheet and transparent communication for the user whenever using the app with an informed consent form clarifying the risks to health and privacy, specifying the possibility of revocation of consent and the destruction of data; specific attention should be given to minors, particularly vulnerable subjects and active users of technology, identifying IT tools for parental control and/or age verification online in order to prepare, accordingly, appropriate and adequate information;
- implementing of informing and educating doctors about mobile-health, in order to allow the acquisition of specific expertise enabling them to use the new IT tools to improve the relationship with the patient in terms

of control and autonomy, mindful of the need to preserve and not to impoverish the interpersonal relationship;
- fostering studies on the impact of the use of apps, with specific attention to the implications on personal and relational identity, in order to clearly identify the problems of technological dependency and vulnerability;
- monitoring an adequate education of particularly vulnerable groups - children, the elderly, the disabled - in order to ensure non-discrimination and enhance inclusion of the advantages in the use of the new technologies;
- social promotion of a critical use of the new applications for health in the context of a balanced relationship with one's own body and health, avoiding forms of excessive health fanaticism and medicalization, focused on the single dimension of health as well-being.

Appendix: Regulation

At the international level[116]

Guidelines

In the USA, the Food and Drug Administration has developed the Guidelines (2011, 2013, 2015) establishing the criteria for the identification of *medical devices,* within the context of apps, distinguishing their regulation according to the different categories[117]. According to the FDA, apps are medical devices if they are used as an accessory to a regulated medical device or transformed as a mobile platform in a regulated medical device. Therefore, if a limited number of apps similar to medical devices (about 100), must in some way be regulated or subjected to a certification path, for all other types of apps, not subjected to this path, certification is not required. However the issues of validity, security and respect for privacy are raised. The FDA speaks of *enforcement discretion*, but not regulation. The FDA believes that if the aim of the application is the management of health in everyday life (thereby excluding it as a medical instrument for diagnosis, care and treatment), and if the risk is low, it does not need to be treated as a medical device. According to US regulations, apps are classified as medical devices, when they act on the structure and functioning of the human body (*to affect the structure or any function of the body of man*). However, some "gray areas" remain which are difficult to assess, with possible diversified uses that could, depending on the context, be classified as medical devices or not. The FDA distinguishes high-risk applications (medical devices), evaluated by a third party and low-risk applications (non- medical devices), validated by the same manufacturer.

A similar approach is followed by the Medicines and Healthcare products Regulatory Agency (MHRA), the agency of the Health Department of the English NHS. This agency has shown a model for classification of clinical apps, which highlights the need to submit to a process of validation only

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[116] A. J. BARTON, *The regulation of mobile health application*, BMC Medicine, 2012, pp. 10-46.

[117] N. G. CORTEZ, J.D., I. GLENN COHEN, J.D., A. S. KESSELHEIM, FDA Regulation of Mobile Health Technologies, "The New England Journal Of Medicine", 2014, 24, pp. 372-379. Mobile medical Applications: Guidance for Industry and Food and Drug Administration Staff, FDA, September 2013, in www.fda.gov, document February 9, 2015.

those apps that are in fact similar to medical devices. The National Health Service reports on the website the apps that have passed a review to prove their safety and compliance with the rules of data protection and security from a clinical standpoint.

A similar initiative in this direction was taken by the Agencia de Calidad Sanitaria de Andalucia with a Catalogue for Mobile Health Applications. A number of countries are turning to the use of guidelines. The Therapeutic Goods Administration, Department of Health in Australia (Australian Government) developed guidelines for health care workers in 2013, including apps in the regulation in force for medical devices.

Regulations/proposals for regulation in Europe

There is no explicit regulation. The applicable regulation in force:

As part of the discipline of medical devices: Directive 93/42/EEC on medical devices, Directive 98/79/EC in vitro diagnostic medical devices, Directive 90/385/EEC on active implantable medical device.

In the context of the processing of sensitive data: Recommendation no. (97) 5 on the protection of medical data, Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data, currently being reviewed[118]. Directive 2002/58/EC concerning the processing of personal data and the protection of privacy in the electronic communications sector, modified by Directive 2009/136/EC. With reference to users also Directive 2011/83/EC on consumers rights.

With reference to par. 38 of the Explanatory Memorandum[119] of the Recommendation no. (9) 5 on the protection of medical data, where the link between medical data and non-medical data is highlighted, for example, lifestyles[120]. In this report, paragraph 61 states that the use and analysis of

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[118] Commission proposal, available at ec.europa.eu/justice/dataprotection

[119] Council of Europe - Explanatory Memorandum on the Recommendation on the Protection of Medical Data. Available at: www.coe.int/t/dghl/standardsetting/dataprotection

[120] "The drafters of the recommendation further agreed that under the terms of the recommendation, 'medical data' should also include any information - unless it is public knowledge - giving a ready idea of an individual's medical situation, for instance for insurance purposes, such as personal behaviour, sexual lifestyle, general lifestyle, drug abuse, abuse of alcohol and nicotine, and consumption of drugs. This was the reason for including in the definition of medical data the words 'manifest and close', that is, having a clear and direct impact on the health situation of the individual".

data should be for therapeutic purposes[121]. In this sense there is discussion on the possibility that the data related to lifestyle may be regarded as medical data.

In the context of European initiatives on this topic refer to:

- Guidelines related to the topic:
- Guidelines on the qualification and classification of stand-alone software used in health care within the regulatory framework of *medical devices* Meddev 2.1/6 January 2012. In these guidelines, the definition of medical device means any instrument, apparatus, application, software, material or other article, used alone or in combination, including the software intended by the manufacturer for specific use in diagnosis and/or treatment, prevention, monitoring, treatment, also aims to relieve pain, harm or compensate for disabilities, for research, replacement or modification of the anatomy or physiological process. Stand alone software is software that is not embedded into a *medical device* at the time of placing on the market. The definition of *medical device* is mainly identified in the intention of the manufacturer (*manufacturer's "intended purpose"*).
- Guidelines on medical devices MedDev 2.7.1 rev 3 Clinical evaluation guides for manufacturer and notified bodies, identifies the documents that a manufacturer must submit to the notified body in the presentation of clinical data that will serve for CE marking and, therefore, all the elements that a notified body itself must take into account when assessing the same clinical data before the CE marking of a medical device. A specific document for the clinical evaluation of coronary stents is attached to Appendix 1 of MEDDEV.
- Guidelines on medical devices MedDev 2.7.2, Guide for Competent authorities in making an assessment of clinical investigation notification (European Commission Enterprise and Industry Directorate General). Lists the documents and the main elements which the competent author-

[121] "In practice, this means that the principles are applicable to the collection or the processing of medical data for the purpose of medical treatment, the assessment of the health condition or the fitness of a person".

ities must take into account during the assessment of clinical investigations notified by the manufacturer.

- Guidelines on medical devices MedDev 2.7.3, Clinical Investigations: serious adverse event reporting (European Commission Enterprise and Industry Directorate General). It specifies how to communicate to the competent authorities any serious adverse events occurring during the conduct of clinical investigations before marketing.
- Guidelines on medical devices MedDev 2.7.4, Guide for clinical investigation- guide for manufacturer and notified bodies (European Commission Enterprise and Industry Directorate General). It specifies the essential elements for the proper planning and performance of clinical investigations of medical devices, as well as providing details of the circumstances in which clinical trials are required.
- Guidelines on medical devices MedDev 2.12/2 rev.2, Post-market clinical follow-up studies-Guide for manufacturer and notified bodies (European Commission Enterprise and Industry Directorate General). It is a guide for the planning and carrying out of post-market studies as part of the plan for follow-up after-sales developed by the manufacturer.
- Guidelines on medical devices MedDev 2.12/1, Medical devices vigilance system (European Commission Enterprise and Industry Directorate General). Illustrates the European system for reporting and evaluation of incidents and corrective actions for security (FSCA) involving devices marked CE, among them those used in clinical investigations after marketing.

- The Warsaw Declaration on the *appification of society* (September, 2013), in the context of the meeting of the Data Protection and Privacy Commissioners 35th annual international conference, raised forcefully the issue of privacy.

- The European Commission has released a "Green paper on Mobile Health" (10 April 2014)[122] with the aim of collecting, with extensive consultation of citizens/ patients, health professionals and manufacturers, their re-

[122] ec.europa.eu/digital-agenda/en/news/green-paper-mobile-health-mhealth.

spective opinions on the different obstacles that prevent a wider spread. A report on the consultation has also been published[123].

- Recently, the Council of Europe, Directorate General Human Rights and Rule of Law, circulated a questionnaire (15 September 2014) Consultative Committee of the Convention for the Protection of individuals with regard to automatic processing of personal data, data protection and medical technologies issues. A consultation was attended by: the Privacy Authority, Ministry of Health, the National Committee for Bioethics, for ethical aspects. The question of m-health in the context of e-health is treated specifically.

- A working group was established (in 2013), art. 29 Working Party on apps (WR29), an advisory body to the European Commission on the topic. In February 2015 the group produced a document which clarifies the definition of healthcare data in the context of applications on lifestyles and well-being. A letter was sent from the Group of European guarantors - addressed to the Commission - on the definition of health data in relation to apps. The annex to the letter reveals some important bioethical reflections. In the annex, please note that the use of healthcare data is prohibited by art. 8 of the Data Protection Directive (95/46/EC), with certain exceptions. Healthcare data are qualified as highly sensitive data that require proper restrictive protection; the misuse of data can be irreversible and result in consequences for the individual. Healthcare data are data about the health of the individual; they are medical data originating in a medical context, however also covering a broader context. Even data correlated to health fall within healthcare data (e.g. the data of those who wear glasses or contact lenses; lifestyle habits such as smoking or alcohol use). Healthcare data are not only data collected when one is "sick" (e.g. the results of blood tests are healthcare data even if one is healthy). One can speak of healthcare data regardless of whether they are the result of tests carried out by doctors or in a medical context. In this sense, the

[123] ec.europa.eu/digital-agenda/en/news/summary-report-public-consultation-green-paper-mobile-health

group notes that the core of the regulation on data protection refers to reasonable proportionality in the collection of data (including *data controller* and *data subjects*): Users must be aware of, the collection of data minimized to actual needs, with the identification of those who collect the data and for what purpose (specific, explicit, legitimate). The group points out that it is not clear whether the applications for lifestyles and fitness are covered by that regulation.

- At the European level, in October 2013 the first European Directory of Health Apps was issued which includes about 200 mHealth apps on an online platform[124].

[124] Available from myhealthapps.net. A further document at theEuropean level specific for the health sector is represented by *eHealth Action Plan 2012-2020: Innovative Healthcare in the 21th Century*, whose aim is to remove obstacles to the full use of digital solutions in the European healthcare systems.

Regulation Proposals

Within the European Parliament there is an ongoing review of the regulation on *medical devices*[125] and the processing of personal data.

The European Parliament on 22 October 2013 adopted a text on the proposal for a regulation Amendment adopted by the European Parliament on 22 October 2013 on the proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) no. 178/2002 and Regulation (EC) no. 1223/2009 (COM 2012/0542 - C7 0318/2012 - 2012/0266 COD)[126].

Within the framework of the protection of personal data the regulation is being revised.

European Parliament legislative resolution of 12 March 2014 on the proposal for a regulation of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation)[127].

At the national level

There is a lack of explicit regulation of m-health. The following can be considered regulatory references:

- Code for the protection of personal data: DL June 30, 2003, no. 196. In Article. 122 "Information collected in respect of the contractor or user" refers to the storage of information and the need for consent with simplified procedures (taking into account consumer associations) and the "use of methodologies that ensure the effective awareness of the contractor and user". For the purpose of the expression of consent computer programs and devices with easy and clear usability should be utilized.

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[125] ec.europa.eu/growth/sectors/medical-devices/documents/revision/index_en.html
[126] www.europarl.europa.eu/sides
[127] www.europarl.europa.eu/sides

- Decree Law October 18, 2012, no. 179, sec. Agenda and digital identity, sect. 12: electronic health records and surveillance systems in the health sector; art. 7 coding systems of data; safeguards and security measures to be taken in the processing of personal data in the interest of the patient; details of allocation of ID code not allowing for direct identification, interoperability criteria at regional, national and European levels.
- Related Decrees and Circulars:

- Legislative Decree 507/92 and subsequent amendments, art. 7 par.s. 1 to 6 and par.s. 8 and 9 and Annexes 6 and 7. Implementation of Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices.
- Legislative Decree 46/97 and subsequent amendments, art. 14 par.s. 1 through 7 and par.s. 9 and 10, and attachments viii and x. Directive 93/42/EEC concerning medical devices.
- Legislative Decree n. 37/10. Implementation of Directive 2007/47/EC amending Directives 90/385 / EEC on the approximation of the laws of the Member States relating to active implantable medical devices 93/42/EEC concerning medical devices and Directive 98/8 / EC concerning the placing of biocidal products on the market.
- Ministerial Decree of 2 August 2005. How to submit documentation for notification of clinical investigation with medical devices.
- Circular of the Ministry of Health on August 2, 2011. Clarification on "mode of submission of documentation for notification of clinical investigation with medical devices".
- Legislative Decree 24 June 2003 no. 211 implementation of Directive 2001/20 /EC on the implementation of good clinical practice in the conduct of clinical trials on medicinal product for human use.
- Ministerial Decree of 21 December 2007. Conditions for issuance of the request for authorization to the competent authority for communication of substantial amendments and the declaration of the end of the clinical trial and the request for an opinion to the ethics committee.
- Harmonized technical standard UNI EN ISO 14155 - 2012. Clinical investigation of medical devices for human subjects. Good clinical practice.
- Harmonized technical standard UNI EN ISO 14971 - 2012. Medical devices- application of risk management to medical devices.
- Ministerial Decree of 12 March 2013. Restrictions, conditions and facil-

ities where one can conduct clinical trials of medical devices, in accordance with art. 14 of Legislative Decree 24 February 1997 no. 46, as amended.

- Initiatives of the Ministry of Health: the establishment of the Directorate General of Digitization and Computerization. It is currently processing and implementing the D.L. 2012 by the Ministry of Health.

- Guidelines of the Data Protection Authority (currently being processed).

Under the "Privacy Sweep 2014" sponsored by the Global Privacy Enforcement Network (GPEN) 25, the Data Protection Authority launched in May 2014 an investigation into medical and wellness applications, downloadable on smartphones and tablets, aimed at assessing the degree of transparency on the use of personal data, the required permissions before downloading and respect of the Italian legislation on the protection of personal data. The survey results, published September 10, 2014, confirmed how even in our country users are not adequately protected and often are not put in a position to express free and informed consent. 50% of Italian and foreign medical and wellness applications analyzed by the Authority, and randomly chosen among the most downloaded available on various platforms (Android, iOs, Windows, etc.), in fact, either do not provide users with an informative sheet on the use of data prior to installation, or give general information, or call for excessive data in relation to the features offered. In many cases the privacy policy is not adapted to the reduced size of the monitor, making it difficult to read, or it is placed in sections concerning, for example, the technical characteristics of the smartphone or tablet.

- Code of Medical Ethics (2014).

The Code - in Title XVIII healthcare computerization and innovation, art. 78 on "Information Technologies" – highlights the requirement of the use of new technologies and the acquisition of consent, the protection of confidentiality, the relevance of the data collected and the security of techniques. The doctor is called upon to "guarantee the conscious participation of the patient". The doctor's use of these technologies for the purposes of prevention, diagnosis, treatment, and clinical surveillance, is to adhere to the criteria of "proportionality, appropriateness, efficacy, and security".

Presidenza del Consiglio dei Ministri



MOTION

INEQUALITIES IN HEALTHCARE DURING AND AFTER CHILDBIRTH: A NATIONAL EMERGENCY

29 may 2015

Overview

The National Bioethics Committee (ICB) sets out to draw the attention of the Institutions and the public opinion to the critical issues related to healthcare at birth to be found in most Italian Regions and which are attributable to the organization of the healthcare system and its facilities. Such critical issues have to be identified, reported, and tackled.

The ICB has already addressed the topic of the issues related to childbirth in various documents, *Coming into the world* (1995), *Pregnancy and childbirth from the bioethical standpoint* (1998), *Premature infants. Bioethical notes* (2008), highlighting, in particular in the Opinion, *Coming into the world*, that the moment of birth, "influenced by the variables of the social and economic system, requires social, juridical and medical protection, in a context of efficient services." The recurrence of tragic events, especially in some southern Italian regions, today highlights the existence of serious issues concerning such protection, making it necessary and urgent to seriously reflect on the different levels of responsibility and on the unequal way in which they arise within the different areas.

Indeed, unfair inequalities in medical assistance at birth in our country seriously undermine the respect for the principle of justice in one of its most important and vital expressions, namely the integration of two fundamental human rights, the right to equality and the right to healthcare, only achievable by means of an equitable distribution of healthcare resources. There is no doubt that the issue of unfair differences in the fruition of the right to health is multifaceted and concerns all those living in Italy belonging to all age groups, and the Committee sets out to suitably analyze this problem in a broader perspective, taking into consideration its different, specific aspects[128]. Nevertheless, such a problem has implications involving a great degree of responsibility in the phase immediately following childbirth; the first moments of life are not only characterized by a particular vulnerability, but are also decisive, in either a positive or negative way, for the future of the person. It is increasingly evident that several adult illnesses, as well as

[128] The Committee has already devoted an Opinion to the issue of equity in the field of healthcare in *Bioethical guidelines for equal access to healthcare*, 25 May 2001, and has more recently drawn the attention to the more specific issue of unfair inequalities in the assistance to elderly women in *The living conditions of women in the third and fourth age: bioethical aspects of social healthcare*, July 16, 2010.

many disabilities, can be induced by adverse conditions during the neonatal period and childhood, which therefore, wherever possible, have to be prevented by means of a rational and equal healthcare policy.

It is also necessary to stress both the importance of such prevention measures during the prenatal period and how the issue of inequalities at birth finds its premises in the care of women's health during pregnancy and very often even before this. There is a precise relationship between conditions of socio-cultural hardship and a higher risk of adverse consequences, which can affect the health conditions of both the mother and the fetus. Several studies show how factors that can particularly affect this are the country of origin, schooling, type of job, obstetric precedents, gynecological precedents, general conditions of health, diet, personal hygiene, as well as the type of dwelling. In particular, women originating from foreign countries where the population is forced to migrate have their first check-ups when the pregnancy is already at an advanced stage, do not do any kind of analysis, do not check blood pressure and weight, and often have bad diets both qualitatively and quantitatively. It thus follows that these women fall ill during pregnancy more than the Italians, with pathologies that are either not diagnosed or reported too late: thyroid disorders, diabetes, nephropathies, vitamin deficiencies, hypertension, and pregnancy-related illnesses. Fetal growth restriction is also frequent, as it is often not diagnosed at an early stage.

Effective prevention measures against inequalities at birth should therefore foresee right from the gestation period:

a) the enhancement of counseling services, which should carry out functions of hospitality, cultural promotion, and socio-healthcare integration;
b) the setting up of childbirth education classes, where women (especially if foreigners) can be informed about the possibilities to receive appropriate assistance from pregnancy to childbirth and homecoming with the baby;
c) the implementation and simultaneous monitoring of the "birth path" (from 2010 State-Regions Agreement), i.e. taking charge of pregnant women from their first examination, with a program providing for the tests necessary to monitor the health conditions of the mother and fetus.

The ICB is thus aware of the extreme complexity characterizing the issue of inequalities at birth, but by means of this motion it sets out to highlight the aspects strictly related to the organizational shortcomings affecting

the period immediately following birth. Indeed, the Committee recognizes that in that period and due to those shortcomings, the right to healthcare is a right that is fulfilled in an unfairly different way depending on the region of birth, which is decided by fate.

Thanks to improved living conditions and medical knowledge in Italy, there has been a significant reduction in infant mortality in recent years, which has reached levels that can be compared to those to be found today in the most developed countries of the western world. Nevertheless, this reduction in infant mortality, of which 70% is represented by neonatal mortality, has not occurred evenly. In the southern regions, it is still higher than in the northern ones by about 30%[129]. The causes of this phenomenon have to be attributed to various factors. In addition to the well-known different weight of economic and social problems, on which it is impossible to dwell here, an element playing a decisive role is the insufficient organization of perinatal therapies and the existence of many little maternity units.

Contrary to what many still believe, the fragmentation of birth centers does not favor the management of emergencies and greatly increases the clinical risk for both the mother and the infant. Very often centers with less than 500 births per year, particularly numerous in southern regions, are not provided with specific equipment and have a staff that is non-specialized and unprepared to cope with emergency situations.

Notwithstanding the provisions of the 2010 State-Regions Agreement, the administrations which established the progressive rationalization/reduction of birth centers within the "birth path" with a number of childbirths lower than 1000/year, find it difficult to close such facilities[130]. Likewise,

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[129] Latest *ISTAT* data, available on the website www.istat.it/it/archivio/14562, relating to infant mortality refer to 2012, as mortality data by age are not available for 2013, but only data on birthrate and neonatal mortality. In 2012 there were 242,388 and 182,922 live births respectively in Northern and Southern Italy; deaths within the 1st year of life were 697 and 704 respectively. The infant mortality rate was equal to 2.88 per one thousand live births in the North and equal to 3.85 per one thousand live births in the South. The infant mortality rate in Southern Italy is 33% higher than the one in the North.

[130] Agreement, pursuant to art. 9 of Legislative Decree no. 281 of 28 August 1997, between the Government, the Regions, the Autonomous Provinces of Trento and Bolzano, the Provinces, the Municipalities, and the mountain communities on the document regarding "Guidelines for the promotion and the improvement of quality, safety, and appropriateness of interventions assisting the birth path and for the reduction of Caesarian sections" (Rep. acts no. 137/CU) (11A00319), available from www.trovanorme.salute.gov.it.

the same Agreement provided for the setting up, completion, and coming into effect of the maternal assisted transport system and the Newborn Emergency Transport Service (NETS), which nonetheless are not yet available in large areas of the country. Due to the lack of a neonatal transport service in many regions and in large metropolitan areas, there is a significant delay in the beginning of therapies, together with a rise in the risk of death during the neonatal stage or the appearance of neurological damage with disabling consequences in newborns delivered in centers lacking the Neonatal Intensive Care Unit (NICU).

It is important that women with high-risk pregnancies give birth in maternity wards equipped with neonatal intensive care units, but it should always be kept in mind that even a normally-progressed pregnancy can unexpectedly get complicated at the moment of birth and engender emergency situations for both the mother and the baby. Hence, each birth center, even if lacking neonatal intensive care units, needs to be able to deal with emergency situations while waiting for transfer to an equipped center.

It should also be noted that NICUs, which amount to a higher number than the recommended standards, are not provided with an equally high number of actually available beds. This is often due to shortages in medical staff and/or nurses or to a lack of space and valid equipment from a technological point of view.

It is a fact that the regions with the most critical healthcare situations are those subject to recovery plans from the regional economic deficit, in which it is not possible to hire new staff or even to replace those retiring. Due to the lack of beds in NICUs, very often even when very premature babies are born in a properly equipped center, they cannot be treated in the same hospital and have to be transferred to another center where a bed in the NICU is available[131]. Such transfers can have serious consequences for the health of the baby, especially for the most critical newborns.

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[131] In the Lazio Region, in 2014, 101 newborns were transferred, due to a lack of beds, from a III level center, i.e. an NICU, to another NICU, of which 96 babies were preterm and 25 had a gestational age of less than 28 weeks (Lazio Region, Directorate of Health Care, Health and Social-Health Care Integration. Neonatal Transport in the Lazio Region 2004-2014), available from www.regione.lazio.it/binary/rl_sanita/tbl_contenuti/Trasporti_neonatali_2004_2014.pdf.

Without an increased efficiency of the NICUs and an improved organization of the perinatal network, neonatal mortality rates in the southern regions cannot be lowered. In the light of the above-mentioned critical issues, it seems appropriate to highlight how, from an ethical perspective, it is inadmissible that the compliance with the different parameters imposed by the recovery plans can impact so heavily on the right to health.

Another inequality in the provision of healthcare to newborns relates to the implementation of the Expanded Newborn Screening, which enables the early diagnosis of more than 40 rare pathologies, many of which are disabling. Today this test is carried out only in some regions of Italy[132], but recent legislative interventions (2014 Stability Law) are expected to solve this problem in the near future. It is also desirable that all birth centers are able to perform the audiologic screening, aimed at an early identification of hypoacusis and deafness, as well as the ophthalmological screening for an early diagnosis of visual abnormalities.

The ICB therefore considers it urgent to draw the attention of the Government, the Regions, and the Autonomous Provinces to the need for a concrete implementation throughout the national territory of the diagnostic-therapeutic-healthcare paths established for birth[133], for a check and a periodic monitoring of the criteria characterizing such paths, as well as for effective and decisive interventions where the regions encounter difficulties in the provision of neonatal medical assistance. As provided for by art. 117 of the Italian Constitution, essential levels of services relating to civil and social rights have to be guaranteed throughout the national territory and it is unacceptable that the respect for budget balances negatively affects the right to health. Hence, it is necessary to stop the trend of differentiation in healthcare provision between the different regions and it is essential to

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[132] From the consultation of the technical report on neonatal screening programs in Italy, drafted in 2013 by the Italian Society for the study of hereditary metabolic diseases and neonatal screening, it comes to light that national coverage is total for hyperphenylalaninemia and congenital hypothyroidism, stable at about 80% for cystic fibrosis and 30% for expanded screening to metabolic diseases, available from www.simmesn.it/it/documents/rt_screening/rt_screening_2013.pdf.

[133] Agreement between the Government, the Regions, and the Autonomous Provinces of Trento and Bolzano, the Provinces, the Municipalities, and the mountain communities on the document regarding "Guidelines for the promotion and the improvement of quality, safety, and appropriateness of interventions assisting the birth path and for the reduction of Caesarian sections" (16 December 2010).

integrate them, in order to guarantee everyone the right to "the enjoyment of the highest attainable standard of health" from the moment of birth, as the safeguard of health is a "fundamental right of the individual and a collective interest" (art. 24, par. 1 of the 1989 UN Convention on the Rights of the Child and art. 32 of the Italian Constitution).

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The document was drafted by Prof. Mario De Curtis, with the contribution of Prof. Marianna Gensabella.

The document, discussed within the plenary, was voted and approved unanimously by those present, Profs. Luisella Battaglia, Carlo Caltagirone, Stefano Canestrari, Carlo Casonato, Francesco D'Agostino, Lorenzo d'Avack, Antonio Da Re, Mario De Curtis, Carlo Flamigni, Silvio Garattini, Marianna Gensabella, Demetrio Neri, Andrea Nicolussi, Laura Palazzani, Massimo Sargiacomo, Monica Toraldo di Francia, Grazia Zuffa.

The ex Officio members who joined are the following: Drs. Maurizio Benato, Carla Bernasconi, Carlo Petrini.

Among those who did not attend the plenary session, the following members adhere to the Declaration: Profs. Salvatore Amato, Rodolfo Proietti

Personal remark

A personal remark by Prof. Cinzia Caporale

The writer of this remark adheres to the idea expressed in the motion according to which it is ethically very relevant to tackle the inequalities in the enjoyment of the right to health which persist in different areas of the country. Such inequalities are increasing among the elderly, but certainly assume a very special significance in the stages immediately following birth, as rightly stated by the drafters.

However, with regard to the specific contents of the motion, the writer wishes to highlight the following:

With regard to infant mortality rates, Italy has lower levels than those of countries like France, Germany, Great Britain, Canada, and the United States and, has rates which place it among the best countries worldwide in the most reliable international rankings.

According to *ISTAT* data, there has been a continuous decrease in infant mortality rates since the 1950s until today throughout the country, with higher percentage decreases in Southern Italy. For example, from 1951 to 2011, the infant mortality rate decreased by about 17 times in the North and about 22 times in the southern Regions.

Notwithstanding the occurrence of more significant improvements in the South, the data still report a higher level of infant mortality in this area. However, considering also the absolute numbers illustrated in the motion (a difference of 7 deaths per year between the North and southern Regions out of a total of 1,401 deaths per 425,310 live births), the interpretation of the data requires a great deal of caution because, as for all socio-healthcare phenomena, there are undoubtedly multiple underlying causes which should be deeply analyzed in order to understand their single and aggregated effects and to assess which of them proves "decisive" within the different contexts. As suggested also by the motion – though in a non-satisfactory way, according to the writer – there are indeed several endogenous and exogenous factors affecting the occurrence of different risk situations at the moment of birth and in the first year of life; medical assistance is just one of the determining causes. Not by chance, infant mortality is normally considered as

an indicator of the persistence of social problems that can be tackled by means of large-scale preventive interventions and actions. In the writer's opinion, it is therefore not possible to adhere to the following statement laid down in the motion: "Without an enhancement of the NICUs and an improved organization of the perinatal network, neonatal mortality rates in southern Regions cannot be lowered."

With regard to the general inequalities between regions and macroareas of the country, in the case of healthcare services, there has been a significant improvement of outcome indicators over time, and specifically in the last ten years. This has been the case for both the national average and, particularly starting from the middle of the last decade, for the southern regions specifically. As a matter of fact, available indicators report a significant improvement in national average data and a process of convergence in service standards guaranteed in the different areas, with a decrease in situations of technical inefficiency. For example, the rationalization of the offer of healthcare services, which came about following the introduction of the Recovery Plans in 2006, has accelerated the shutdown process of marginal facilities throughout the country, concentrating the birth centers within a relatively limited number of units and increasing the conditions of technical efficiency and levels of effectiveness, assessed on the basis of outcome indicators. Such improvements have to be mentioned and underlined, albeit some critical issues persist and need to be overcome, particularly in the southern regions.

Overall, available data do not support the argument according to which the 2001 federal reform would have brought about an increase in the differences concerning healthcare outcomes among regions. Conversely, the constant monitoring of the adequacy of expense levels with respect to efficient benchmarks has introduced a permanent pressure towards the improvement of both organizational solutions and service levels. In other words, once the homogeneity of the criteria defining the essential levels of healthcare services was ensured, the existence of a differentiation between areas has represented a positive push towards the improvement of service levels and standards of technical efficiency. In any case, in the writer's opinion, the evaluation of the Recovery Plans and the specific economic aspects regarding healthcare policies falls outside the competences of the National Bioethics Committee.

Presidenza del Consiglio dei Ministri



MOTION

ON THE IMPLEMENTATION OF REGULATION (EU) NO.536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL OF 16 APRIL 2014 ON CLINICAL TRIALS ON MEDICINAL PRODUCTS FOR HUMAN USE, AND REPEALING DIRECTIVE 2001/20/EC.

25 September 2015

The European Union has approved a new Regulation to streamline the rules for the authorisation and carrying out of clinical trials in the Member States.

• The ICB puts forward a number of considerations with regard to this[134].

The Regulation sets down in art. 4 that "a clinical trial shall be subject to scientific and ethical review" and that "the ethical review" shall be performed by an ethics committee in accordance with the law of the Member State concerned, and may encompass, according to the cases, aspects addressed in Part I of the assessment report for the authorisation of a clinical trial as referred to in art. 6 and in Part II of that assessment report as referred to in art. 7.

It must be considered that in Part I there are not only scientific aspects but also aspects of an ethical nature (therapeutic benefits, the importance of clinical trials, the reliability and robustness of the data generated in the clinical trial, the risks and inconveniences for the subject, etc.) and in Part II aspects linked to the protection of subjects and the requirements for informed consent, as established in Ch. V of the Regulation and in relation to the territory of the Member State in question.

Nevertheless, the combined provisions of such norms is not so explicit and an interpretation of the Regulation can also be made that is in favour of the choice on the part of the State of a separation between the scientific and ethical aspects to be allocated separately, the former to scientific committees and the latter to ethical ones.

The ICB highlights the risks of this possible separation and recommends that the single national committee or ethics committees for clinical trials deal with the review of both aspects concerning art. 6 (Part I) and those related to art. 7 (Part II).

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[134] The ICB has already expressed its opinion on the regulation in the Motion "*ICB Declaration on the document "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 (17 July 2012)"*, 31 October 2012. It also gave its opinion on clinical trials in previous opinions. Among these in particular: *Clinical trials in adult or minor patients who are unable to give informed consent in emergency situations,* 28 September 2012; *Pharmacological trials in developing countries*, 27 May 2011; *The improper use of placebo,* 29 October 2010; *Bioethical problems in clinical trials with non-inferiority design*, 24 April 2009; *Pharmacological trials on women*, 28 November 2008.

In this motion we set out to stress the reasons for this recommendation.

Undoubtedly there are aspects that must be considered strictly ethical: that the controlled clinical trial is carried out in such a way as to defend the interests of the patients balancing the foreseeable risks and benefits, that the patient gives his/her informed consent, that the patients are insured against any possible harm, that there are no conflicts of interest, etc.. Moreover, as generally happens in research, such interests shall be essentially defended by making sure that the protocol satisfies significant requirements for which the trial is worth carrying out and that the modalities whereby the study is conducted makes it possible to achieve valid conclusions.

More in general the ethics committees must ascertain that the interests of industry, science and society do not prevail over the wellbeing of the subject[135]. It is also just as important to verify that the methodology of the study is in line with ethical principles. Special attention must be paid to what is stated as a general principle in art. 3 of the Regulation: a clinical trial may be conducted only if the rights, safety, dignity and well-being of subjects are protected and prevail over all other interests, as well as being designed to generate reliable and robust data. And again it stresses the importance of monitoring and inspections foreseen by the Regulation in arts. 48 and 78.

For this reason the ICB strongly reaffirms the inseparability of the scientific aspects from the ethical principles. Science and Ethics are closely connected and cannot be separated, without the risk of the revival of a dichotomy that was overcome decades ago both at a theoretical and operational level by the ethics committees present in the research institutes and healthcare facilities all over the world, Italy included.

- The organisational aspect of the ethics committee, referred by the Regulation to the single States in the respect of a number of very precise requirements (e.g. for the persons charged with assessing and validating the application in art. 9, with the obligation to respect a strict timing and to express one single decision), can lead to different solutions: a single

[135] Among the many documents on this, see the *Convention on Human Rights and Biomedicine*, 1997, art. 2 *and Declaration of Helsinki*, October 2013, arts. 3-4.

national ethics committee; national ethics committees in a limited number for specialised subject areas; ethics committee of national/international reference and coordination for the territorial and/or sectorial ethics committees.

Among the various above mentioned solutions which all present problematic profiles that translate into advantages and disadvantages, for the formulation of the "single opinion" the ICB proposes the setting up of an ethics committee for clinical trials – with appropriate facilities – with the function of reference for Italy at the international level and coordination of a limited number of territorial and/or sectorial ethics committees with competences for therapeutic areas for the assessment of national and international trials[136].

Wherever relevant, such committee can take the assessment upon itself also availing of external experts.

Among the advantages of this option:

a) The presence of a national ethics committee of reference at the European level and of reference for the territorial and/or sectorial ethics committees for clinical trials, and should it be necessary, able to assess and validate the application
b) The ethical review can each time be entrusted to the territorial and/or sectorial ethics committee presenting the best competences for the proposed research, without having to continuously gather experts
c) The experiences of the territorial and/or sectorial ethics committees for clinical trials are preserved and its further specialisation is promoted
d) Italy could enter the network that – at the European level – unites the States that have already achieved the coordination of their ethics committees.

For the purpose of guaranteeing the respect of the deadlines established by the Regulation, the ICB recommends that the number of territorial and/or sectorial ethics committees for clinical trials be reviewed and limited.

[136] In this context the territorial and/or sectorial committees refer to the committees only for clinical trials and not to the committees for the assessment of clinical cases.

In this such way the ethics committee of reference and coordination for clinical trials could easily take on the role of an efficient, authoritative observatory, able to communicate with the other ethics committees. It must be taken into account that in the respect of the Regulation it is not just a question of examining the traditional bioethical (and bio-juridical) profiles posed by the single clinical trials, but it is necessary to search for the origin of the bioethical issues and, therefore, to have the competence to seek possible solutions, even the most complex ones or those most difficult to identify.

The close connection between the scientific and ethical dimensions advocated above must be confirmed by the necessarily interdisciplinary composition of the ethics committee of reference and coordination and the territorial and/or sectorial ethics committees whose members, taking into account gender differences, must have ethical, scientific and juridical competences. It is necessary that the members of these committees, as foreseen in the Regulation (art.9) are guaranteed the requirements of independence and transparency, do not have conflicts of interest, are independent of the sponsor, as well as free of any other undue influence. They must be appointed according to the principle of "impartiality" according to transparent criteria. The assessment report cannot be made by anyone who must then use the data of the controlled studies for regulatory reasons or to assess reimbursement by the National Health Service (NHS).

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The text was drafted by Profs. Lorenzo d'Avack and Silvio Garattini.

The debated text was voted on and unanimously approved by those present in plenary sitting: Profs. Salvatore Amato, Luisella Battaglia, Stefano Canestrari, Lorenzo d'Avack, Antonio Da Re, Riccardo Di Segni, Paola Frati, Silvio Garattini, Assuntina Morresi, Demetrio Neri, Andrea Nicolussi, Laura Palazzani, Rodolfo Proietti, Monica Toraldo di Francia, Giancarlo Umani Ronchi.

The members without the right to vote expressed their approval: Dr. Maurizio Benato (Federazione Nazionale degli Ordini dei Medici Chirurgi e degli Odontoiatri) and Dr. Carlo Petrini (Istituto Superiore Sanità).

Profs. Carlo Caltagirone, Cinzia Caporale, Carlo Casonato, Bruno Dallapiccola, Francesco D'Agostino, Mario De Curtis, Carlo Flamigni, Marianna

Gensabella, Massimo Sargiacomo, Lucetta Scaraffia and Grazia Zuffa were absent in the plenary session but endorsed the motion at a later date.

The motion was also endorsed by Dr. Carla Bernasconi (Federazione Nazionale Ordine Veterinari Italiani), Dr. Rosaria Conte (Consiglio Nazionale delle Ricerche) and Dr. Anna Teresa Palamara (Consiglio Superiore Sanità).

Presidenza del Consiglio dei Ministri



DEEP AND CONTINUOUS PALLIATIVE SEDATION IN THE IMMINENCE OF DEATH

29 January 2016

Introduction

The subject was initially brought to the attention of the Committee by Prof. Francesco D'Agostino; at a later date Hon. Paola Binetti posed a query (given in the attachment) inviting the Committee to go into the ethical aspects of deep sedation in more depth, asking in particular whether or not it can be distinguished from euthanasia.

Deep sedation is an issue that is linked to the subject of palliative care, which the Committee dealt with in the opinion *Pain therapy: bioethical guidelines (2001).* In drafting the opinion the Committee puts forward a number of reflections with the aim of clarifying the definition and ethical conditions of deep sedation at a theoretical level, as well as offering practical guidelines for healthcare professionals.

The Committee criticises the expression "terminal sedation" which is used in literature owing to the ambivalence and imprecision that it conveys and proposes the terminology "deep and continuous palliative sedation in the imminence of death" to indicate the intentional administration of drugs, in the dosage required, to reduce to the point of annulling the patient's state of consciousness, in order to alleviate pain and the physical and/or psychological refractory symptom which has become intolerable for the patient in the imminence of death.

The ICB identifies a number of conditions that are ethically indispensable for the carrying out of deep sedation: an incurable illness in an advanced state; imminent death; the presence and assessment of one or more refractory symptoms or acute terminal events with intolerable suffering for the patient; the informed consent of the patient. The procedures for the application of deep sedation require proportionality, the monitoring of drug usage and the entering of the procedures in the medical record.

The Committee addresses the distinction between deep sedation and euthanasia and for this purpose, procedures and outcomes, considers that deep and continuous sedation, which is continued until the patient's loss of consciousness, must be recognised as a healthcare treatment and not confused with euthanasia or assisted suicide or consensual homicide.

The question of the patient's informed consent is specifically dealt with, as well as advance care planning, also relying on advance statements about medical treatment, deep sedation in pediatric patients and the professional training of healthcare workers.

In its final recommendations the Committee stresses that it is a fundamental right of the dying person (adult or child) to receive adequate support aimed at controlling suffering in the respect of their dignity. Particularly with regard to children, the Committee recommends that the parents be suitably informed and supported on the issues linked to deep and continuous sedation and that the best interests of the child are respected and that their will is respected too within all possible limits.

Lastly, a full application and integration of Law no. 38/2010 will hopefully be implemented, regulating palliative care and pain management in Italy, since unacceptable inequalities are found among regional areas.

The opinion includes two appendices: a normative and a technical/medical one.

The opinion contains a personal remark by Prof. Carlo Flamigni and a statement by Prof. Demetrio Neri, explaining the reasons for their dissent from the document.

The group was coordinated by Prof. Lorenzo d'Avack, who supervised the drafting with the contribution of Profs. Rodolfo Proietti and Laura Palazzani.

A number of experts were invited to give their professional advice on the subject during the plenary session including Prof. Carlo Peruselli, President of the Italian Society for Palliative Care (26 June 2015), Prof. Rodolfo Proietti, full professor of anaesthesiology and reanimation at the Catholic University of the Sacred Heart (25 September 2015) and Prof. Ferdinando Cancelli, palliative care physician (25 October 2015).

The document was debated in the plenary sessions of 20 November, 11 December 2015 and 29 January 2016, and approved with votes in favour by the members: Amato, Battaglia, Canestrari, Caporale, Casonato, D'Agostino, Dallapiccola, Da Re, d'Avack, De Curtis, Di Segni, Frati, Garattini, Gensabella, Morresi, Nicolussi, Palazzani, Proietti and Toraldo Di Francia and voted in favour by the advisory members: Benato, Bernasconi and Petrini. The members Flamigni and Neri voted against the document and Zuffa abstained.

Caltagirone, Scaraffia, Sargiacomo and the advisory members Conte and Palamara were absent at the voting but endorsed the opinion at a later date.

Lorenzo d'Avack

1. Preamble

The ICB has already dealt with end-of-life issues on various occasions[137]. In tackling this subject it has deemed it appropriate to place great attention on palliative care and pain management, understood as cure and care, aimed at managing the patient's physical-psychological suffering and social support, in order to improve their "quality of life" in the respect of their "dignity". It also had the opportunity to reaffirm that the fight against physical-psychological pain comes into the primary tasks of medicine and society.

In the opinion *Pain therapy: bioethical guidelines* (2001), the promotion of hospital facilities and hospices was recommended in an attempt to move towards the "hospital without pain", professional training courses for healthcare workers, and the widespread diffusion of information on this to citizens.

It stated that, in taking into account the will of the patient and their concept of life and health, healthcare workers should assess pain control in light of the idea of "quality of life" that every person has the right to formulate for his or herself. It was stressed once again how pain management came into those rights, and which the citizen can ask to be respected and fulfilled by the competent bodies. These are rights that must come into the healthcare guaranteed by art. 32 of the Constitution and which must be fully taken into consideration in the promotion of human rights. In other words, pain control was already highlighted as being an integral part of what a person can and must expect from medicine and healthcare professionals. An excellent reason to recommend that pain control should fall under the "essential and uniform levels of healthcare".

With its attached recommendations, this opinion had a decisive impact on the modification of the regulations regarding palliative care and pain management in force in Italy: Law no. 38/2010 'Provisions guaranteeing the access to palliative care and pain control'. Nevertheless, even though this law made reference to pain control in all stages of the illness, particularly in the advanced and terminal ones, it is necessary that this

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[137] ICB, Opinion on the *Draft Resolution on assistance to the terminally ill*, approved by the Committee on the Environment, Public Health and Consumer Protection of the European Parliament, 30 April 1991; *Bioethics with childhood*, January 22, 1994; *End-of-life issues in bioethics*, July 14, 1995; *Pain therapy: bioethical guidelines*, March 30, 2001.

fundamental right of the patient (adult or minor) to receive suitable support aimed at the management of physical-psychological suffering with the aim of improving the quality of life in the respect of their dignity and will is actually carried out.

At the same time, an increased awareness in the medical profession is required with regard to the value and efficacy of palliative care, also in the terminal stages of life. In fact the law alone is not sufficient if at the same time a new approach to patients suffering is not asserted. While it is true, as specified later on, that deep sedation has specific characteristics with respect to palliative care and pain control, it is also evident that the development of these practices is connected to the establishment of a widespread medical culture that is capable of looking at the patient's suffering as an integral part of the illness that the doctor is called upon to treat.

The fact that there is still a lot to do is also demonstrated by the world data on opiates used in medicine, underlining their underuse in Italy.

Indeed, not everything foreseen by the laws in force has so far been fully realised in organisational and professional terms. Report to Parliament on the state of implementation of Law no. 38/2010 of 2015 highlighted that there is a noticeable difference between what is possible and dutiful to do and what in practice is actually done. This is all the more so that during the last decade palliative care has developed to such a degree as to represent a new discipline in medicine and presupposes the organisation of treatment and assistance that is taking on great importance in the world, also because the epidemiological scenario of the population of the developed countries is changing; life expectancy is growing exponentially every year and consequently the number of people affected by chronic-degenerative pathologies is increasingly rising, in the advanced or terminal stage of which palliative care represents a fundamental support for patients and their next of kin. In 2014 the WHO unanimously approved a document that commits all states to developing palliative care and sets it down as a fundamental human right[138]. In the same year the WHO also published, together with the Worldwide Palliative Care Alliance (WPCA), the *Global atlas of palliative care at*

[138] WHO Resolution EB134.R7., *Strengthening of palliative care as a component of integrated treatment within the continuum of care*, January 2014.

the end of life[139], in which an estimate is given of the global number of adults needing (or who might need) palliative care in the terminal stages of life as being over 19 million.

There is therefore a widespread awareness that an attempt is being made in this care to give efficient answers to the real needs and rights of the population.

For this reason, the Committee deems it appropriate to return to end-of-life situations with this document, focusing on the problem of deep and continuous sedation in palliative care: this reflection will take into account the ethical issues arising from this, the progress in medical science, common practice and the need to implement a number of normative aspects.

2. Terminology and definition of the practice

Within the general context of palliative care, generally speaking palliative sedation consists in the intentional reduction of the patient's consciousness to its possible phasing out, in order to alleviate the physical and/or psychological refractory symptoms.

The administration of palliative sedation can be carried out in different ways:

- *moderate/superficial*, when it does not completely take away consciousness or *deep*, when it comes to the phasing out of consciousness;
- *temporary* (if for a limited time), *intermittent* (if administered alternately, according to the oscillation of circumstances) or *continuous* (if extended until the death of the patient).

In its various modalities, palliative care is given to a patient with an advanced incurable disease.

Herein the Committee sets out to refer to palliative sedation in the specific modality: deep, continuous, with impending death. The imminence of death refers to the condition of expecting death in a lapse of time ranging from a few hours to a few days, according to the diagnosis and prognosis of the medical team.

The expression 'terminal sedation' is often used in literature. The Com-

[139] Worldwide Palliative Care Alliance (WPC), World Health Organization (WHO), *Global atlas of palliative care at the end of life*, 2014.

mittee considers that it is an expression that should not be used as it creates ambiguities[140]. The adjective 'terminal' can be used to indicate the final stage of life (agonic stage with inevitable evolution towards death). Or it can be used to say that by means of such treatment an end is put to the patient's life. Lastly, the definition could be referred only to the irreversible nature of the sedation.

The Committee proposes the terminology "deep and continuous palliative sedation in the imminence of death" to indicate the whole procedure, bearing in mind the above mentioned distinctions, like "the intentional administration of hypnotic drugs in the required dosage, in order to reduce the level of consciousness to the point of phasing it out, to alleviate or take away the perception of an intractable physical or psychological refractory symptom, which would otherwise be intolerable for the patient, in a condition of incurable terminal illness close to death".

In order to understand this therapeutic treatment a definition of "refractoriness of the symptom" is also needed, given that this circumstance is, together with the patient's consent, priority to legitimate deep sedation. While there is the complex task of defining the concept of refractoriness of a symptom, above all in consideration of situations not only strictly physically but also psychologically stressful, the ICB makes reference to the one in the Recommendations of the Italian Society for Palliative Care (SICP): "The refractory symptom is one that cannot be adequately controlled despite aggressive efforts to identify a tolerable and efficient therapy practised by an expert and that does not compromise consciousness"[141]. Among the most frequent refractory symptoms are dyspnea, intractable distress, nausea and persistent vomiting, delirium, psychomotor agitation, psychological or existential distress. A number of indispensable conditions are to be observed in this definition. In all the clinical situations that require deep sedation, it is of vital importance to first of all verify the actual refractoriness of the symp-

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[140] The Italian Society for Palliative Care (SICP) in its document *Recommendations of the SICP on terminal sedation/palliative sedation* (2007) also highlights the ambiguousness of the adjective "terminal", which can "be understood both as a prognostic element referred to the stage of illness and as a definition referring to the irreversibility of the sedation".

[141] Italian Society for Palliative Care (SICP), *Recommendations, op. cit.*, p. 10. (See Technical/medical appendix to the Opinion).

tom by assessing that: a) its control cannot be achieved through an adequate and proportionate dosage of drugs (the lowest level of sedation able to alleviate the refractory symptom, with the least number of negative side effects); b) any different or further non pharmacological treatment is not able to guarantee relief to the patient or relief such as to make the suffering tolerable within an acceptable time. Both the clinical and ethical appropriateness of the choice depend on this diagnosis. Therefore, the state of refractoriness of a symptom must be ascertained and monitored by a team of palliative care experts made up of physicians, nurses and psychotherapists. The use of drugs must always be monitored and appropriate to the depth, continuity and duration of the sedation and an accurate record together with documentation entered into the patient's medical record should be kept of the clinical case and the degree of sedation reached[142]. For the purposes of an assessment of the decision-making process and its application, a retrospective evaluation of the way in which the sedation was carried out is undoubtedly useful and to be recommended. This retrospective record should allow all the actors involved to understand on which basis the treatment was decided and what the controversial aspects have been, in order to improve the understanding of such situations in the future.

From the experience gained over many years of palliative medicine in different countries (United Kingdom, France, Switzerland, Italy, Spain etc.) it is considered that a protocol for deep and continuous sedation can be adopted in the presence of a number of pivotal events: - the patient's informed consent; - an incurable illness in an advanced stage; - impending death, generally expected within a few hours or days; - the presence of one or more refractory symptoms or acute terminal events with intolerable distress for the patient. These circumstances must be present simultaneously in order to legitimate the treatment from an ethical point of view.

The bioethical question also arises from the relationship between the starting of deep sedation in the above described conditions and the suspension of treatment constituting therapeutic continuity in the care of the terminally ill, guaranteed by means of the continuity of the vital functions

[142] See art. 7, Law no. 38/2010, where the obligation is foreseen to enter the detection of pain in the medical record.

supported artificially (e.g. oxygen therapy, hydration, artificial feeding, etc.).

The Committee points out that as far the connection is concerned between 'deep sedation' and the need/duty to suspend all the vital support therapies, each case must be judged singularly, taking into account that many of these treatments are symptomatic and necessary in order to alleviate suffering. It is important that the patient is monitored regularly and does not undergo disproportionate and needless interventions.

With particular reference to hydration and nutrition, in most of the patients in the imminence of death, artificial nutrition/hydration is not indicated owing to the serious concomitant changes of the metabolism. Furthermore, a patient that is still able to feed and hydrate him/herself or for whom nutritional and/or hydration support is prescribed and received cannot normally be treated with deep and continuous sedation insofar as death is not likely to be expected within a short time.

3. Deep and continuous sedation in the imminence of death and euthanasia

The ICB stresses from the very start that in this opinion it does not set out to deal with the ethical problem posed by euthanasia or assisted suicide or consensual homicide. It sets out to consider, at a descriptive level, whether the use of sedative drugs up to the loss of the state of consciousness to give relief to unbearable suffering in the last hours or days of life (deep and continuous sedation in impending death) can be considered an act of euthanasia.

There are differences between the two situations, already outlined and unanimously approved in the context of palliative care[143], which place deep sedation and euthanasia on two different levels. The journal "*European Journal of Palliative Care*" of 2003 published a piece of work by the European Association for Palliative Care (EAPC)[144] in which it was highlighted that, at the level of objectives, outcomes and procedure, sedation and euthanasia are two different cases. On 19 November 2015 the EAPC confirmed this

[143] Differences formalised among others by the European Association for Palliative Care in 2003.

[144] *Euthanasia and physician-assisted: a view from an EAPC Ethics Task force*, 2003, 10, pp. 63-66.

standpoint in a "*White paper*"[145] which updates the previous 2003 document.

With regard to the objectives, procedures and outcomes, sedation is a therapeutic act having as its goal the alleviation or elimination of the distress and suffering of the dying patient through the management of the refractory symptoms, while euthanasia, according to the definition most widely used today, consists in the administration of drugs which with the patient's consent are aimed at bringing about their immediate death.

From the medical literature it appears that the average survival rate of sedated terminal patients does not differ from that of patients who are not sedated and some research carried out in 2003 showed that patients sedated for over one week before dying, in conditions of serenity and placed in a condition of greater stability from a physiological point of view, survived longer with respect to those not sedated[146]. A systematic review on the subject of deep palliative sedation was published in the *Cochrane Review* confirming that patients sedated in this way do not have a lower survival rate with respect to those not sedated[147].

Deep sedation therefore is not indicated as a treatment that shortens life, if applied appropriately, and cannot be considered as an act directed at death.

4. The patient's consent

By the expression "institutions" is meant the whole set of subjects that in various ways intervene in the process of "government" of drug administration and which have the responsibility of guaranteeing the quality and safety of clinical treatment: National Health Service, the Health Ministry, the Superior Institute of Heath, AIFA, hospital facilities, ethics committees, doctors and judges.

It must be highlighted that Law no. 38/2010, even though referring to

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[145] L. RADBRUCH, C. LEGET, P. BAHR, C. MÜLLER-BUSCH, J. ELLERSHAW, F. DE CONNO, P VAN DEN BERGHE, *Euthanasia and physician-assisted suicide: A white paper from the European Association for Palliative Care*, "Palliative Medicine", November 19, 2015.

[146] N. SYKES, A. THORNS, *The use of opioids and sedatives at the end of life*, "Lancet Oncology", May 2003, 4(5), pp. 312-318.

[147] E. M. BELLER *et al.*, *Palliative pharmacological sedation for terminally ill adults*, "Cochrane Detabase Syst Rev.", January 2, 2015, 1.

the autonomy of the patient, does not tackle the specific problem of information and consent to palliative care.

For deep sedation, a part of palliative medicine, one cannot forego a therapeutic approach model centred on the patient as the protagonist of treatment and informed consent therefore seems to be a fundamental element of the care relationship. To speak of consent in these situations does not of course mean signing a document, as much as rather letting the patient's awareness with respect to their prognosis grow and embracing their desires, in the context of the patient/doctor treatment relationship. The decision-making process must be stated in the therapeutic alliance, between patient/family and patient/healthcare operators and such alliance should lead towards not only an informed consent, but also a shared one. In fact, rather than the acquisition of consent to specific painkilling treatment, the reaching of a basic agreement is considered fundamental, or the search for a 'shared trust' on the basis of a number of desires, life choices, values manifested by the patient and gained within the relationship with the healthcare professionals. The decision to begin deep and continuous sedation should therefore be characterised by proceeding cautiously, guaranteed by a number of opinions in a shared decision, and taken at the end of exhaustive information given on the evolving seriousness of the symptoms of the terminal stage, the objectives and modalities of sedation, with explanations at clinical and ethical levels.

In the explanation of the procedure it is important to anticipate the answer to questions that are asked most frequently so as to reduce the risk of incomprehension or misunderstandings to a minimum. It is necessary that the consent is personalised, considering that each case is presented differently and that the patient's desires and their possible changes during the illness are respected[148]. Just as it must be considered that patients can voluntarily refuse deep sedation. It is clear that suffering and pain are perceived subjectively and the individual can attribute a religious sense or nevertheless a personal feeling to it or may want to maintain a contact with the world surrounding them or live the moment of death all the way.

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[148] With regard to this, see the modalities for a consent modulated on the needs of the single case: Italian Society for Palliative Care, *Information and progressive consent in palliative care: a shared evolutionary process,* Recommendations of the SICP, 2015.

It must be underlined that the will and desires expressed in the consent are even more difficult to ascertain in the end-of-life situations in which deep palliative sedation is proposed, where the presence of refractory symptoms or the previous attempts at pain sedation with narcotic painkillers can lead to the clouding of consciousness, consequently hindering the patient's capacity to express their last will and to communicate with others. The subject of consent and end-of-life choices thus entail the need to face the question of advance directives for medical treatment within the patient-doctor collaboration, a subject already dealt with by the Committee[149]. Here it is important to recall the "Guide on the decision-making process regarding medical treatment in end-of-life situations" (Council of Europe, DH-BIO, 2015) which states: "Regardless of the legal scope of advance directives in any given legal system, they will always have more weight in the decision-making process if they correspond to the actual situation and are drawn up in the light of a specific medical context. This is the case of the patient who finds him/herself in the condition of understanding the consequences of his/her illness". Therefore, before situations in which the patient's consciousness is failing with the consequent hindrance to the capacity to express their last will, the Committee considers it opportune that the value of the advance directives be recognised *w*ithin the shared advance care plan.

Even though in the first place the patient must give their informed consent, and should they not be able to give consent, this must be given by whoever legally represents them or by their next of kin, the decision to resort to sedation must always be a therapeutic decision shared by the healthcare team who thus assume the relative responsibilities for this in the same way as they would for all the other therapeutic decisions taken in the course of medical care.

Lastly, it is stressed that also the patient, who refuses treatment or various types of treatment or who refuses to make use of instrumental support techniques of the vital functions, entering an end-of-life process, has the right to benefit from pain control and, should there be refractory suffering, to deep and continuous sedation[150].

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[149] ICB, *Advance treatment statements,* December 18, 2003.

[150] ICB, *Conscious refusal and renunciation of healthcare in the patient-doctor relationship*, October 24, 2008.

5. Deep sedation of pediatric patients

Pediatric patients pose particular problems with respect to adults concerning pain and sedation.

It must be recalled that when one speaks of minors one is referring to a wide category of different subjects. Children's incurable illnesses are very different from those of adults (the haemato-oncological ones are fewer than 25-30%) differing form each other and are often characterised by an "undulatory" course, with sudden unexpected worsening and improvement, whereby the stage of supposed "terminality" cannot always be identified with certainty. It must always be considered that pain in children can bring about short and long term negative effects and influence their behaviour, cardiovascular and neuroendocrine system and the prognosis. It is therefore vital to avoid painful procedures as much as possible and rather treat the pain safely and effectively[151].

As far as children are concerned, there has been a growing tendency over the years to include them in the decision-making about their care. The Code of Medical Deontology sets down that the doctor should give the child the most appropriate information for diagnosis, prognosis, the prospects and possible alternative diagnostic-therapeutic interventions planned for the purpose of involving them in the decision-making process (art. 33) and shall duly consider the opinions expressed by the minor in all the decision-making processes regarding him/her (art. 35). Nevertheless, the possibility that the minor, still at a very young age, can uphold his own autonomy at a practical level seems difficult to realise. It must be added that the course of the illness, pain and death of a minor, especially if not a new born baby, is different for the family and doctors involved in their care with respect to that of an adult. The medical history of a child who cannot be saved from death gives rise to complex psychological and emotive mechanisms involving and conditioning the family and the medical staff themselves. These are among the main reasons for which a communication relationship is established between the medical team, the sick child and their family, characterised by ongoing dialogue and an open exchange, whereby thanks to this alliance the best interest of the minor is achieved and, as far as possible, the respect of their will.

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[151] See the *Charter of the Rights of the Dying Child - The Trieste Charter*, 2014.

In its Opinion *Bioethics with childhood* (1994), the National Bioethics Committee put forward a series of reflections and recommendations with regard to the involvement of the child in therapeutic care. As far as the treatment of children is concerned ethics committees were advised to always seek the consent/dissent of the child over 7 years of age together with that of the parents and to consider the consent/dissent of the adolescent of 14 upwards obligatory and overriding with respect to that of the parents.

Considering also the changes in the reaching of maturity and awareness of children recorded by the human and social sciences and the variability of the psycho-social conditions, it is necessary to invoke flexibility when considering these suggestions which represent useful guidelines rather than regulations. "Nevertheless – writes the ICB – it is certain that children and adolescents are subjects of knowledge, that is more or less evolved and with an infinite number of attributes during their development, with an ongoing need for profound respect… It must always be remembered that even the very young child has a peculiar cognition of himself and his sick and suffering body that cannot be reached by adultomorphous cognitive schemes and has processing mechanisms of kinesthetic corporeal experiences, which are equal to the knowledge systems attributed by adults in a chronological increase"[152].

This is all the more reason therefore why each critical patient in the pediatric age group must have a care plan that will identify and give adequate pain control and, should it be necessary, sedation to reduce agitation and distress. The treatment administered must be appropriate with respect to the patient's needs and the extreme goal of deep sedation should be specific for each different case. Even the measuring of pain is a standard of care to be applied with validated methods, suited to the age and type of patient and represents the best indicator of efficacy of the ongoing treatment. It is nevertheless necessary to bear in mind that in children there are other distressing symptoms as well as pain, such as dyspnea, convulsions, psychomotor agitation, which when refractory need sedation to relieve the suf-

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[152] ICB, *Bioethics with childhood*, January 22, 1994, p. 57.

[153] S. POSTOVSKY, B. MOAED, E. KRIVOY, R. OFIR, M. W. BEN ARUSH, *Practice of palliative sedation in children with brain tumors and sarcomas at the end of life*, "Pediatr. Hematol. Oncol.", September 2007, 24(6), pp. 409-415.

fering[153]. This type of palliative sedation is theoretically and in practice not necessarily irreversible and can be reduced and suspended according to the child's needs.

Art. 7 of Law no. 38/2010 states the obligation to enter the presence of pain in the medical record. Scientific literature on the subject shows that even before the age of 3 evaluation instruments can be used in which the child associates his/her own pain with photographs or drawings that represent different degrees of joy and pain[154].

In the same way as for adults, the aim of the pain management must be defined a priori and redefined in time in compliance with a care plan and dialogue with the family must follow the same communication logic foreseen in the other cases for capable or incapable adults. Also in these cases the aim of the communication is to give information and involve the next of kin. In this regard the family must be helped to understand and possibly share the motivations leading the healthcare professionals to propose such treatment. The parents must have an adequate amount of time to discuss their opinions and feelings and to ask questions.

From both an ethical and juridical point of view, a particular problem might arise if the parents are opposed to deep sedation therapy being carried out on their child. It must be highlighted that parents have a responsibility towards their children, which is that of taking care of their fundamental interests. The guarantee of what remains of a life without suffering in these dramatic situations and the respect of dignity until death are two essential parameters in identifying what is best for the child. In the case of disagreement between doctors and parents over these decisions, it can be helpful to have the opinion of the pediatric ethics committee when possible[155].

It must also be considered that in the pediatric age group there are not many readily available painkillers that are suitable for children and hence the need to make recourse to *"off label"* therapies; although complicating

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[154] Wong/Baker Faces Rating Scale, Oucher Scale.

[155] See art. 37 of the Code of Deontology where it states with regard to children: "In the case of opposition by the legal representative to the necessary and undeferrable treatment of minors or those lacking capacity, the doctor must inform the judicial authority; if there is a danger or serious risk to the health of the minor or the incapable, the doctor must nevertheless proceed without undue delay and in accordance with the need for indispensable treatment".

the problem even more so from a bioethical point of view, such need can never represent a formal pretext to deny adequate sedation for children.

6. Hospice and professional training

Training is needed in the individual construction of reflection and collegial discussion so that each healthcare professional might deal with more and more frequent complex situations involving a number of ethical aspects in clinical practice. Both in the contexts of the initial training and ongoing professional training, the focus must be on the importance of the learning of teamwork processes. The training should also be extended to all those involved in end-of-life care (nurses, psychologists, social workers, religious assistants). Lastly, specific studies are recommended that take into account the complexity and peculiarity of the situations that arise and which are often the result of advancements in medicine and medical techniques. These studies on decision-making processes should encourage interdisciplinary approaches, linking human sciences and medicine and fostering the development of ethical competences.

Law no. 38/2010 sets down the outline for the realisation of a structured system, aimed at guaranteeing even highly complex socio-healthcare responses over the entire country, which, as such, presuppose the adequate training of the personnel having to interact during the course of treatment.

In such a viewpoint, in parallel with the definition of pain control and palliative care networks, it has been made possible to benefit from the training courses foreseen by the above mentioned law to allow the various professional categories to look more in detail at the specific clinical-healthcare competences and to broaden the planning and management capacities of the integrated diagnostic-therapeutic courses. With this goal a specific "palliative care" discipline has been set up, in which deep sedation is included and the categories of the professionals involved in this are defined[156].

Nevertheless, the application of the above legislation is far from being satisfactory at an operational level by the Regions, with unacceptable in-

[156] In particular with the State-Regions agreement of 7 February 2013 was identified, for the professional category of physicians – Area of diagnostic medicine and services – the discipline of "palliative care" for the purposes of public competition rules for the access of doctors to facilities set up to be part of the palliative care network.

equalities among regional areas to be found. In fact the actual application of the Italian law does not follow the traditional North-south divide, but has the outline of a patchy inhomogeneous map. Even the universities in Italy have done little for the application of art. 8 of the law which foresees masters aimed at training suitable professional figures to work in the sector with inevitable negative outcomes on the quality of the care given to the patients.

A specific reference must be made to the pediatric world. Art. 5 of the law foresees hospital and regional services with professional figures that have specific competences and experience in the field of palliative care and pain management for pediatric patients.

However, just as in adult care, likewise for the treatment of children there are regional differences and pediatric palliative care is generally insufficiently diffused over the country[157]. Most of the children who are down for palliative care die in inadequate conditions, without the necessary relief from painful symptoms, usually in hospitals and rarely in dedicated residential facilities (pediatric hospices)[158]. Children in the terminal stage of illness, which may lead to the need for deep sedation, must be cared for and assisted in an environment in keeping with their age, have all round and continuous care, must be able to express and see their emotions, desires and expectations being embraced and must have their family and those dear to them suitably assisted in the organisation of the treatment.

Generally speaking, in the management of palliative care and in particular deep sedation are embodied the traditional ethical principles guiding

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[157] At present only nine Regions have formally approved the setting up of the pediatric network of CPP + TDP (Basilicata, Campania, Emilia-Romagna, Liguria, Lombardy, Piedmont, Umbria, Veneto and PP. AA. of Trento and Bolzano) and only five of these (Basilicata, Emilia-Romagna, Liguria, Lombardy and Veneto) have actually created it. Only in Veneto is there a pediatric hospice and only five Regions have set up at least a Reference Centre with a multi-disciplinary team, dedicated to the paediatric palliative care (CPP) (of which four are in the north: Emilia Romagna, Lombardy, Piedmont and Veneto; there is only one in the south: Basilicata).

[158] Even if in Italy there are no official numbers regarding the presence of children in need of palliative care, on the basis of forecasts, it can be calculated that every year there are about 11,000 minors (age 0-17) with incurable pathologies. A survey carried out in the Veneto Region shows that in Italy there are 15,000 children needing a palliative care approach and that half of these need specialist palliative care or, that is, the ongoing intervention of professionals exclusively dedicated to pediatric specialist care working in specific multi-professional teams. At present only a small part of these children can benefit from this appropriate palliative care (Commission for pediatric palliative care, in www.salute.gov.it/imgs/c_17_pubblicazioni_580_allegato).

clinical decisions: non maleficence, beneficence, informed consent and equity. It is fundamental that such principles are used in the best interest of the dying person or whoever is suffering. Nevertheless, in this question the unbalanced attention by medicine still seems to prevail to the objectives of care and recovery with respect to palliation and the relieving of the pain and suffering caused by the pathology. Not sufficient account is taken of the fact that a good end-of-life care is possible and that painful death is avoidable. This is serious since it is in this very context that the bioethical aspects can enter into conflict with the organisational ones. In fact, the insufficient diffusion of palliative care in Italy, for both adults and children, which is patchy with macroscopic differences from region to region, generates intolerable and unfair inequalities clashing with the principle of justice.

The Committee is aware that the problems of an ethical, deontological and social order are all the more delicate and complex the more extremely vulnerable people are being dealt with who are between life and death. These are situations that can bring about deep changes in the life of the dying persons and their families and/or in which the patient's dependence on the healthcare personnel is "maximum", as in the case of an incurable child close to death. Therefore the management of these particularly vulnerable people needs to be entrusted to professionals expert in the sector of this specific palliative care, who are suitably trained under the bioethical profile, able to identify and always keep in mind what the best thing to be done and the best treatment for the dying patient is.

It is important that the staff dealing with end-of-life situations is part of a therapeutic team already acquainted with the patient and his family insofar as this can facilitate the transition, undoubtedly not without distress, from needless curative treatment to deep and continuous sedation, avoiding the mistaken interpretation of therapeutic abandonment.

7. Recommendations

The Committee:

1. Considers that it is legitimate to adopt a deep and continuous sedation protocol in the presence of three contextual situations: - incurable illness at an advanced stage; - imminence of death, generally expected within a few hours or days; - presence of one or more suitably assessed symptoms

refractory to therapies or of acute terminal events with serious physical and psychological distress.

2. Stresses that it is a fundamental right of man and therefore of the dying person (adult or minor) to receive adequate support aimed at the control of suffering in the respect of their dignity. Therefore, even though the legislation in force (art. 2, Law no. 38/2010) makes explicit reference to pain management in all the stages of the illness with particular reference to the advanced and terminal stages of the same, it is necessary that the patient's right is actually enforced. Also the patient, who becomes part of an end-of-life process following their refusal or retraction of one or more treatments or the use of instrumental support techniques of the vital functions has the right to benefit from pain control and continuous and deep sedation in the case of refractory suffering.
3. Reaffirms that for the goal, procedures and outcomes, continuous deep sedation, which is extended to the loss of the patient's consciousness, must be considered a healthcare treatment and not confused with euthanasia or assisted suicide or consensual homicide.
4. Deems a suitable amount of information necessary for the patient's informed consent, given in progressive and modulated terms, also in advance with respect to the progression of the illness.
5. Considers it appropriate that, before situations in which the patient's consciousness will fail in the long run, consequently hindering their capacity to express their last will, value be given to advance statements within the shared care plan.
6. Recommends that the parents be suitably informed and supported concerning the issues linked to the deep continuous sedation of pediatric patients. It is essential that good communication is established between the dedicated medical team, pediatric patients and their families, characterised by continuous dialogue and open exchange. The best interest of the minor is priority and their will must be respected too, within all possible limits.
7. Considers it necessary that for all cases of deep sedation the decision must be suitably justified and entered into the medical record, as expressly foreseen also by art. 7 of Law no. 38/2010.
8. Recommends a specific and ongoing training also in bioethical issues of the healthcare professionals who deal with this terminal stage of the patient. The training should involve also specific studies of medical records

of previous cases in order to gain awareness of the complexity and peculiarity of the situations, without neglecting the study of advances in knowledge on deep sedation. Interdisciplinary research should be encouraged, linking the human and medical sciences.

9. Looks forward to the full application and integration of Law 38/2010, which governs palliative care and pain management in Italy, since unacceptable inequalities among regional areas still abound.

NORMATIVE APPENDIX

- In the 90s norms existed in Italy which, introduced to limit the use and abuse of drugs, had hindered the prescribing and application of efficient painkillers and in particular opiates and this lasted until the changes introduced by Law no. 12 /2001.
- The National Healthcare Plan 1998/2000 (D.P.R. July 1998) considered it necessary to intervene with actions aimed at an enhancing of antalgic therapies, as well as a development of palliative care for terminal patients, with particular attention to oncological cases.
- The Decree of the Health Ministry of 28 September 1999 (National Programme for the creation of palliative care facilities) foresaw the realisation of hospices; the setting up of the assistance network for terminal patients; the assessment of care quality; the definition of regional competences in this regard.
- The State-Regions Agreement of 2001 envisaged the Hospital without Pain project of which various versions were to appear and which is mentioned in art. 6 of Law no. 38/2010. This project was insufficiently put into effect, despite the fact that at the time of the agreement guidelines had been drawn up for the Regions aimed at adopting the necessary proceedings in order to spread the philosophy of the fight against pain both in facilities for hospitalisation and treatment and in the out-patient care processes.
- The National Healthcare Plan 2003/2005 extended the category of patients involved in palliative care also to non-oncological ones. Furthermore, many concepts were also adopted which were already in the definition of palliative care published by the WHO[159] and by the European Association for Palliative Care (EAPC) and particularly important aspects were highlighted. Among others, "to review a number of normative aspects regarding the use of painkillers, improving the availability of opiates, simplifying their medical prescription, lengthening the therapy cycle and making their use possible at the patient's home too".
- Law no. 38/2010 is at present the organic set of regulations on palliative care. In art. 1 it foresees "the right of the citizen to access palliative care and pain therapy", and identifies two separate care networks, one for pain

[159] WHO, *Definition of palliative care*, available from www.who.int/cancer/palliative/definition/en/.

and one for palliative care dedicated to adults and a single network that includes both pain management and palliative care for children dedicated to patients in the pediatric age group. It very clearly underlines how the healthcare facilities delivering palliative care and pain control must guarantee an individual care plan for the patient and their family, in the respect of the fundamental principles for the safeguard of the dignity and the autonomy of the sick person, without any discrimination; of the safeguard and fostering of quality of life at every stage of the illness, in particular in the terminal one; and of an adequate healthcare and socio-healthcare support of the patient and their family. Art. 2 of the law, in mentioning national palliative care networks and pain therapy, makes explicit reference to pain management in all stages of the illness, with particular reference to the advanced and terminal stages of the same, even if deep sedation is not explicitly mentioned (art. 5, par. 3).

- With regard to pain therapy this law must be accompanied by the Single Text of the laws on drugs and psychotropic substances, prevention, care and rehabilitation of the relative states of addiction. The Single Text has been changed and integrated on numerous occasions over the years. In fact, this law simplifies the prescribing of non-injectable drugs; the NHS doctors are thus allowed to prescribe these drugs by using the simple NHS prescription format.
- The Agreement of the permanent Conference on Relations between the State, the Regions and the autonomous Provinces of Trento and Bolzano of 16 December 2010 on the "guidelines for the promotion, development and coordination of the regional interventions within the network of palliative care and pain therapy", established that specifically dedicated facilities should be created dedicated to the coordination of the palliative care and pain management network[160].

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[160] On this subject the Italian Society for Palliative Care, *Recommendations on terminal sedation/palliative sedation* (2007) made a number of recommendations. In the same way also other international organisations like the European Association for Palliative Care, at a later date produced a series of important documents. In 2013 upon initiative of the Fondazione Lefebvre D'Ovidio Onlus the *Charter of the rights of the dying child (the Trieste Charter)* was published. Even the Code of medical deontology in this 2006 version and the more recent 2014 one explicitly attributes the task to the doctor of not only giving treatment aimed at the recovery of the patient, but also to give him relief in suffering and accompany him to his death (arts. 3 and 39).

- The agreement between the Government, the Regions and the autonomous provinces of Trento and Bolzano of 25 July 2012 sets down the minimum requirements and the organisation modalities necessary for the accreditation of the assistance facilities for terminal patients and palliative care and pain control units, and also sets out the identification of the network facilities[161]. The minimum requirements and organisations needed for the accreditation of the residential, home, hospital and territorial facilities are thus defined, identifying qualitative and quantitative standards for the drawing up of the organisation models for the treatment of adults and children in palliative care and pain management.
- The State-Regions conference agreement of 10 July 2014 identifies the professional figures that can operate in the palliative care and pain management networks and in pediatric palliative care and pain control. The agreement set down the contents of the training courses foreseen for the various professional figures.
- The stability and agreement Law of 22 January 2015, contextually with the drafting of the Agreement of 10 July 2014 through a parliamentary passage that overcame the critical issue relative to the doctors who work in the regional palliative care networks without being in the possession of a specialisation, who were therefore excluded from the application of the regulation. For this purpose, the State-Regions Conference adopted an agreement on 22 January 2015 whereby the outline of the Health Ministry decree was approved setting down the criteria for the certification of the three-year experience in palliative care.

[161] By pain therapy network is meant a functional aggregation of pain management activities, delivered in different healthcare settings with the goal of improving the quality of life of the people in pain and to reduce their degree of disability.

TECHNICAL-MEDICAL APPENDIX

Assessment of level of sedation and drugs used.

There is no unanimous agreement on the choice of sedation scale, even if, for practical use, the use of a simple scale is to be preferred, easily applicable and reproducible in different contexts. The most widely used ones are the Rudkin and the Ramsey Sedation scales.

Scale of Rudkin
1st level: patient awake and oriented
2nd level: drowzy but arousable
3rd level: eyes closed but responsive to verbal stimuli
4th level: eyes closed but responsive to physical stimuli (not painful)
5th level: eyes closed and unresponsive to physical stimuli

Scale of Ramsey
1st level: if awake patient is anxious, agitated or restless
2nd level: if awake patient is cooperative, oriented, tranquil
3rd level: if awake patient is responsive to commands only
4th level: if asleep patient has brisk response to light glabellar tap or loud auditory stimulus
5th level: if asleep patient has sluggish response to light glabellar tap or loud auditory stimulus
6th level: if asleep patient has no response to light glabellar tap or loud auditory stimulus

By deep sedation is meant either the 4-5 level of the Rudkin Scale or 5-6 level of the Ramsey Scale.

The choice of drugs

To date the first choice for drugs and the most commonly used is midazolam (short-acting benzodiazepine) even if other drugs can be used such as diazepam or propofol.

The opiates (morphine, fentanil, remifentalin) are not indicated for

their mainly analgesic affect. If they are already being administered to treat pain, they must not be suspended but associated with the sedative-hypnotic drug.

The dosage of the drug used must be quickly increased until it reaches the therapeutic goal and changed according to the varying level of sedation so as to avoid inopportune awakening or an excessive depth of sedation.

Refractory symptom

A symptom that cannot be adequately controlled despite every effort to find an effective therapy that does not compromise the state of consciousness.

The most frequent symptoms defined as refractory in impending death are:
- dyspnea
- *delirium*
- psycho-motor restlessness
- nausea and uncontrollable vomiting (as in intestinal occlusion)
- pain
- psychological or existential distress.

The refractoriness of a symptom must be assessed by a team of physicians expert in palliative care and pain management.

A personal remark by Prof. Carlo Flamigni

The necessary premise to my dissent concerns our specific activity, which is one of reasoning over bioethical issues and not one of finding or endorsing juridical stratagems that allow citizens to avoid criminal sanctions for having chosen a type of behaviour that is considered morally licit by the conscience of most people. In the case in point the problem concerns the doctors and their relationship with euthanasia: we are well aware that this is a choice that is made by many healthcare professionals in a great number of public and private facilities, and which stops being a choice if the doctor feels himself observed, something that can quite normally happen in some institutions. To establish that to take away a person's life must be considered

an illicit and criminal act, even if it is a question of easing the departure of a human being torn apart by suffering that is destined to go on until their death, even if the person asks us to do this as an act of mercy, it is up to the law, and in Italy the law prohibits euthanasia and punishes compassionate doctors. Finding the way to disguise euthanasia by making it pass as a necessary deed, compassionate and licit, is a possible operation, and praiseworthy from certain points of view, but which should not concern us, as we ought to entrust it to the knowledge of the scholars of law or to the imagination of politicians.

In very simple terms therefore, the document takes into account the fact that a definition of death exists; that giving death is prohibited (and punished) by the law; that continuous deep palliative sedation does not hasten (perhaps) death and is not therefore forbidden by law. I would like to make some observations on this point.

Continuous deep palliative sedation should be used only in the imminence of death, and this entails the need for a definition, which is impossible to give in medicine; I have seen people with a prognosis of a sudden and very close death (all the doctors smile when Mimi's doctor sings "The consumption only leaves her a few hours to live"). I ask therefore: seeing that medicine has no certainties and is based on statistics, which Gauss curve and which standard deviations are we referring to? And shall we propose a different one for each morbid condition? And after how long can justice intervene and demand that the sedation be interrupted? And what are the consequences of this, considering that waiting times of a number of years can be envisaged with what appeals and delays?

Second point. On several occasions at the beginning the document refers to an intervention aimed at improving the quality of life ("…. In the light of the quality of life" "aimed at improving the quality of life"). In my opinion the quality of my life has one judge only and that judge is me: but if I am unconscious and will never have my consciousness back again, I cannot give this judgement, either for good or for worse. If, during the course of continuous deep palliative sedation you torture me, you do not worsen the quality of my life, I am not there to perceive the harm that you caused me and I will never wake up to be able to experience it. The word life refers to the possibility for participation or the hope for participation, things that are both absent in the case in point: I am alive if I have awareness of myself (or

I will have awareness of myself) if I can (or will be able) to remember my past, imagine my future, reason with you…I am not alive if all that remains of me is the most vulgar part of my biology, the beard that grows, the intestinal peristalsis: my being alive is witnessed by my voice saying rational and sensible things, not the noise of my stomach rumbling.

Third point. In the debate the problem of the administration of drugs was dispatched by stating that in the case in point they do not shorten survival. Where is the evidence for this? No drug is without effects on at least one of the functions of the organism, they are all harmful in some way or other. Aspirin included. In order to affirm that these drugs are absolutely incapable of shortening life, double blind studies are needed on a huge number of patients, above all if we imagine the complexity of the problem and its modifications (undoubtedly not macroscopic) induced by sedation. I believe that it is only fair to admit that one possibility of interference with the duration of life exists, but that this is a question of a very short time. How short? A minute? What is the tolerance, after how much time do we have to admit to having shortened an existence? One minute? An hour? More? And why? Is it not true that even a single minute of our existence is precious (I have heard a very well-known bioethicist say this)? This embarrassing question should be sufficient to convince a magistrate to open an inquiry into continuous deep palliative sedation.

Last point. Palliative care is mentioned on various occasions in the document. I looked up the term *to treat* in the Italian dictionaries and I found more or less the same definitions:

- To give the sick person the therapies necessary for recovery;
- To fight a morbid state with therapeutic means.

I seem to recall a position that has long been held by the Catholic bioethicists who held that MAP is not medical treatment as it modifies the condition of sterility and that therefore it should not be carried out in hospitals. I imagine that it could be maintained that continuous deep palliative sedation is not a treatment, taking into account the meaning of the term *treatment*. And if it is not treatment then what is it? And which facility or institution is really suitable for the treatment of these patients? Perhaps it would be better to gloss over this.

Well then, if I am a patient who is going through hell because of an illness which has no hope of recovery, if I know that this suffering will continue, interspersed with more or less long periods of consciousness, if I fall asleep, each time that the morphine has its temporary effect, terrorised by the idea that I will wake up tormented by my suffering; and yet if someone advances the hypothesis of continuous deep palliative sedation and proposes it to me, what I understand is that I am being offered the possibility to choose a good death and I accept it happily, astonished rather by the fact that Italy has finally legalised euthanasia.

After all, this document, which finally makes a compassionate act legal (but does it with an enticing hypocrisy) and allows many doctors working in intensive therapy facilities to be able to practise without having to fear justice, is from a practical viewpoint a very good thing, with the only defect of being voluntarily forgotten by ethics, which is a very bad choice if we recall the name of our Committee.

Carlo Flamigni

Statement by Prof. Demetrio Neri

This Note does not set out to be an annotation to the document "Continuous deep palliative sedation in impending death". It is just a declaration in support of the negative vote that I cast on the above mentioned document.

As will be remembered, in the December sitting I had proposed the elimination of the whole third paragraph of the document, pointing out that deep sedation is a morally appreciable practice owing to its intrinsic features and does not gain, or lose anything, by being descriptively different from other practices like euthanasia, assisted suicide or consensual homicide. My proposal was rejected by the assembly. I take note of this, but it has put me in the position of not being able to approve the document. The basic reason is that to the question that the ICB sets out to debate in this paragraph (in lines 140-143) my answer is: yes, deep sedation is an act of euthanasia and I – and this is not just recently – am convinced that it – together with, and not with the exception of, other actions – is a good thing that it is part of the group of options available to individual end-of-life choices, in such a way that whoever asks for it, or agrees when it is proposed, can do so because

it corresponds to their moral choices and not because it is the only available option. It could also be pointed out that, at the beginning of the third paragraph, the document chooses to not take into account the ethical problems linked to euthanasia or assisted suicide or consensual homicide, confining itself to describing the objective differences existing among these three practices and deep sedation. Nevertheless, admitted that (but not conceded: see below) the discourse manages to keep within these descriptive limits, I asked myself what use the mere description of the factual differences could be (which moreover, as such, nobody is doubting) between deep sedation and the other above practices. To answer the question posed by Hon. Paola Binetti? It is difficult for me to think that when Paola Binetti asks us to clarify the "boundaries" that separate deep sedation from euthanasia she has in mind purely factual, descriptive "boundaries". To reassure the doctors that in applying deep sedation they are not carrying out an act that can be defined euthanasic? But – as remarked in the assembly debate – the doctors would rather be reassured that they are not carrying out an act that can be defined as a crime and in our legal system there is no specific crime of euthanasia. They should be remanded on the crime of consensual homicide; but – apart from the difficulty, shown in the doctrine and jurisprudence, of attributing euthanistic facts to this crime – I do not think that tasks of such a nature concern the ICB. In any case, this specific juridical aspect has been set aside for some time now. Therefore the document could have done without this paragraph and the moral appreciation of deep sedation and the study of its proper application modalities would have had nothing to lose.

I now move on to clarify why I wrote the above "permitted, but not granted". Even though I appreciated the effort to keep at a descriptive level (I stress however, to avoid any misunderstandings, that I intend – and I have always intended – such "descriptive plan" as that of the various moral standpoints, not that of the factual differences of the acts and facts), I am convinced that in these issues it is inevitable that judgement values creep in, which it might be a good idea to make plain (descriptively) rather than conceal referring to the simple description of the factual differences between deep sedation and the other above mentioned practices. As such the description contains nothing that makes it possible to conclude that the first is appreciable and admissible at a moral level (I shall not deal with the legal level) and the others are not. A value judgment needs to be added to the de-

scription and this is inferred from the decisive choice made by the palliative care movement in favour of palliative care and deep sedation and to the exclusion of active euthanasia upon the patient's request or assisted suicide. See with regard to this point 7.2 of the SICP document, referred to on more than one occasion in the ICB's document: it says that the distinction is made "both at empirical (clinical) level and ethical level" (my italics). This previous, and selective at moral level, decisive choice is also to be found in the ICB's document: or, at least, it is difficult to infer it. For example, in lines 117-121 are listed the four circumstances that must be present simultaneously in order to "ethically" legitimate deep sedation; but the same circumstances can accompany the case of a patient who refuses deep sedation and asks to be given a substance that puts an end to his life. Why would those circumstances, in themselves considered and descriptively speaking, "ethically" legitimate the first and not the second? It seems to me that the only difference lies in the different orientation of the person, but this has nothing to do with the descriptive and factual level, but with the existential plane of the life choices and values of that person. If, in the presence of the three other conditions, the request/consent of the patient is morally acceptable only if it is already (descriptively?) framed in what the medical profession considers what can or not be done, what is the point of speaking further on, in the paragraph on informed consent, of "embracing their desires" (line 173) or to seek "a shared trust based on a number of desires, life choices, values manifested by the patient" (lines 177-178)? It would appear, and selectively so, only those desires, life choices and values can be embraced that come into the group of those that the medical profession considers to be ethically acceptable, and is there not a value judgement going on here? In all this are we still on the descriptive plane? Actually, the text just referred to is completed with "and gained within the relationship with the healthcare professionals" (177-78). Now apart from the fact that it seems rather limiting to speak in terms of desires and, even more so, of choices and values (which are or should be those that are gained in the course of a whole lifetime), the sentence seems to want to say that only those desires, life choices and values can be considered that the patient gains within the context of the relationship with the medical team, perhaps changing those previously held. If this is the right interpretation, the passage comes to mind in which Plato (I am not able to find the quotation) suggests that doctors

should establish with their patients (only the "free" ones and not the slaves) what today we would define as a communication relationship: but with the aim of "making them docile and law-abiding by rhetorical means": this is a most "insidious" form of medical paternalism!

Allow me to add an observation on another point of the document which (among others, of lesser importance) does not convince me. At the end of the second paragraph is the question about the relation between deep sedation and the interruption of other treatments. According to some (and I am among those) the giving of deep sedation necessarily requires the interruption of other treatment (see, for example, the recent French law), but the document states that "each case must be judged singularly, taking into account that many of these treatments are symptomatic and necessary in order to alleviate suffering". According to me it is not easy to understand what this means; if it is decided, with the patient's consent, to use continuous deep sedation because with the other treatments the distress and suffering cannot be eliminated, what is the point, in deep sedation, of continuing to administer treatment that has evidently been inefficacious? And moreover who decides, as the patient is in deep sedation? And on what bases? With regard to artificial hydration/nutrition, it just says that when the patient is at the end of their life this treatment is generally contraindicated (from the clinical point of view I suppose) and when instead it is indicated (always clinically I presume) the patient is not dying and is not eligible for deep sedation. This is a way to bypass the crucial point and that is (as was brought to our attention in one of the hearings) whether the patient wants or does not want to undergo this treatment; clinical appropriateness or inappropriateness does not equal moral appropriateness or inappropriateness (as instead is sometimes stated in the document).

Demetrio Neri

ATTACHMENT:

Question posed by Hon. Paola Binetti to the National Bioethics Committee

To the National Bioethics Committee

To the kind attention of the President
Professor Francesco Paolo Casavola

And copy forwarded to the Vicepresidents:
Professor Lorenzo d' Avack (substitute Vicepresident)
Professor Riccardo Di Segni
Professor Laura Palazzani

Preamble

Law no. 38 of 15 March was enacted in **2010** concerning "Provisions to guarantee the access to palliative care and pain therapy" (Official Gazette no. 65 of 19 March 2010). As it is largely recognised, this is a very innovative law, which for the first time guarantees the access to palliative care and pain therapy by the sick person, in the context of essential levels of healthcare, for the purposes of ensuring the respect of dignity and autonomy of the human being, the need for health, equity in access to assistance, quality of treatment and its appropriateness to specific needs. Among the first in Europe, in art. 1 the law safeguards "the right of the citizen to access palliative care and pain therapy", and identifies three assistance networks dedicated to palliative care, pain therapy and children with medical illnesses. The law stresses very clearly that the healthcare facilities supplying palliative care and pain management must guarantee an individual care plan for the patient and their family, in the respect of the fundamental principles of the safeguarding of the patient's dignity and autonomy, with no discrimination whatsoever; the safeguarding and promotion of the quality of life in every stage of the illness, the terminal one in particular, and an adequate socio-healthcare support for the patient and their family.

As is well known the law changes the Single Text of the law on the subject of drugs and psychotropic substances, prevention, care and rehabilita-

tion and the relative states of addiction (DPR 309 of 1990), simplifying the prescribing of these drugs by using the simple NHS prescription. At the same time ,however, the Agreement of the permanent Conference on Relations between the State, the Regions and the autonomous Provinces of Trento and Bolzano of 16 December 2010 on the "guidelines for the promotion, development and coordination of the regional interventions within the network of palliative care and pain therapy", established that specifically dedicated facilities should be created dedicated to the coordination of the palliative care and pain management network.

When it mentions national palliative care networks and pain therapy, art. 2 of the law makes explicit reference to pain management in all its stages of the illness, with particular reference to the advanced and terminal stages of the same, clearly envisaging the possible access to forms of deep sedation.

To quote it says: *"The national network for palliative care and the national network for pain management, to ensure the continuity of care of the patient from the hospital facility to their home and includes the whole offer of territorial healthcare facilities, hospitals, the professionals and diagnostic and therapeutic interventions available in the Regions and autonomous Provinces, dedicated to the provision of palliative care, pain management in all the stages of the illness, with particular reference to the advanced and terminal stages of the same, and to the support of the patient and their next of kin";* and later on in art. 4, par. 2, it states: "*The campaigns referred to in par.1 shall promote and diffuse awareness of the importance of palliative care in the public opinion, also pediatric palliative care, and pain management, for the purposes of fostering the culture of fighting against the disease and the overcoming of the prejudice relative to the use of drugs for the treatment of pain, illustrating the fundamental contribution for the protection of the dignity of the human being and the support for the patients and their next of kin".*

The real question

In these times of parliamentary debate it is repeatedly asked by a number of MPs of different parties, in office and in opposition, to schedule the numerous draft laws presented during the XVII legislature, which have as their central theme the so-called Living will, and which was long debated in the previous legislatures, in particular in the XV and XVI. Some of these

draft laws explicitly ask the Italian law to acknowledge also the various requests for euthanasia, along the lines of what is happening in other countries outside Europe too. In this question a number of colleagues maintain that the law on palliative care, approved five years ago, making forms of *pain control possible in all the stages of the illness, with particular reference to the advanced and terminal stages of the same* (deep sedation), already constituted a sort of opening in this sense. Instead this was peremptorily excluded during the parliamentary debate of Act 38 on palliative care, as can easily be seen from the proceedings relative to the approval of the law itself. I therefore ask for a clarification of the boundaries that separate the administration of drugs, as foreseen by Law no. 38, for complete pain control, until its suppression, from possible forms of euthanasia that instead clearly and directly aim at the suppression of the patient. I also ask for the ethical reasons for deep sedation to be specified with particular attention to the patient's informed consent and the decision-making modalities when the consent has not or cannot be expressed. Having at the time presented a draft bill on palliative care and been rapporteur in the House on the same law I would be particularly interested in having an answer from the ICB before going back to scheduling bills which issue precise requests for euthanasia, as well as speaking about the so-called living will.

Sincerely
Paola Binetti
MP, member of the XII Committee

Presidenza del Consiglio dei Ministri



MANAGING "INCIDENTAL FINDINGS" IN GENOMIC INVESTIGATIONS WITH NEW TECHNOLOGY PLATFORMS

17 March 2016

Introduction

In this new document on human genetics the ICB deals with the bioethical issues raised by the rapid evolution of second generation genome sequencing techniques, which over the recent years have transformed and speeded up research on and the diagnosis of many illnesses. These new techniques have posed the need for new shared guidelines and, in particular, standardised regulations for managing the so-called incidental findings, both at clinical and research levels.

Following a description of the state of the art, the ICB goes over a number of crucial ethical steps of the debate with particular reference to the discussion on the theoretical foundations of the "right not to know" in a genetic context.

Even though aware that this transition from basic knowledge to clinical applications is characterised by a high degree of uncertainty and by knowledge that runs the risk of getting outdated in a short space of time, the ICB highlights some of the requirements for the genetics centres and the laboratories carrying out such tests. It stresses that the uncertain demarcation of the line between research and its clinical applications must never let one lose sight of the fact that the diagnostic tests are primarily aimed at giving a diagnosis to the patient, whose needs must remain at the centre of the investigation, and thus recommends that the patient/sample are included in a research project only when the diagnostic investigation has been concluded (either positively or negatively).

Furthermore, it recommends that the traditional distinction is made between adults and minors in clinical investigation and research and that the "best interest" of the subject, not yet able to give their own consent, is placed under a particularly careful assessment. It is also recommended that, upon coming of age, the minor is contacted and able to choose to give/not give their consent to the further conservation of their samples and data (as already highlighted in the Opinion *Pediatric biobanks*).

As far as concerns the question of the returning of information to the donors of biological samples for research purposes, the ICB considers that, in the case of research foreseeing the gathering of large samples, it is unrealistic to contact the donors to update them on the results, which to date would

hardly have any clinical significance of single interest. On the other hand, it considers that if requested it is morally dutiful to guarantee the return of the results of clinical relevance (incidental findings included) to patients with rare diseases and still without a certain diagnosis, always leaving the possibility of opting only to know some types of information to the individual.

Lastly, the ICB stresses that the central role played by genetics and genomics in the healthcare panorama makes it increasingly urgent to rethink the training of the professional figures committed to this field of medicine and, at the same time, the organisation (starting from the school) of initiatives at various institutional levels aimed at citizens, in order to foster the acquisition of the necessary knowledge, which equally includes bioethical knowledge, so as to actively and critically tackle these transformations.

The Working group was coordinated by Profs. Monica Toraldo di Francia and Bruno Dallapiccola, who prepared the draft of the document.

The following took part in the drafting of the document and in particular Profs.: Silvio Garattini, Carlo Petrini and, in the working group discussion, Salvatore Amato, Carlo Casonato, Rosaria Conte, Lorenzo d'Avack, Antonio Da Re, Demetrio Neri, Laura Palazzani, Grazia Zuffa.

The group met for the first time on 19 June 2014 and, after various meetings, the Opinion was debated in the plenary session on 26 February 2016.

The expert advice of Prof. Dallapiccola was given on "The point on personalised medicine (genomic analyses of complex illnesses)" and by Prof. Alberto Piazza.

The document was approved by the members present, Profs.: Amato, Battaglia, Canestrari, Caporale, d'Avack, Da Re, De Curtis, Di Segni, Flamigni, Frati, Gensabella, Morresi, Neri, Nicolussi, Sargiacomo, Scaraffia, Toraldo Di Francia, Zuffa.

The members without the right to vote expressed themselves in favour Drs.: Benato, Bernasconi, Conte, Petrini.

Profs. Caltagirone, Casonato, D'Agostino, Dallapiccola, Garattini, Palamara, Palazzani, Proietti endorsed the Opinion at a later date.

Lorenzo d'Avack

Preamble

Over the years the ICB has dedicated numerous documents to the theoretical evolution and clinical repercussions of human genetics; even though maintaining their bioethical validity today, these documents can be interpreted as successive updates of issues and problems inherent to the rapid developments of this discipline. Some of the titles include: *Bioethical guidelines for genetic testing* (1999), *From pharmacogenetics to pharmacogenomics* (2006); *Genetic testing and insurance* (2008)[162]; *Collection of biological samples for research purposes: informed consent (*2009*)*[163], *Pediatric biobanks* (2014). In 2010, the document *Genetic susceptibility testing and personalised medicine*[164] was published, on the applications of genetics to the safeguarding of health in multifactorial disorders and the first steps of the so-called "personalised medicine" (today the term "precision medicine" - PM is preferred), able to "*directly recognise the individual variability in the relationship between genetic structure, environmental factors, lifestyle and the individual's biographical history*". The ICB deemed it appropriate to recall the contents of this detailed and structured document, which represent the background framework of the new opinion. The 2010 document is divided into two sections, dedicated respectively to the *Scientific aspects of the susceptibility tests in complex adult diseases and the concept of personalised medicine* and the *Standards for good clinical practice, genetic counselling, deontological aspects, of bioethics and forensic medicine*, integrated by conclusions and bioethical recommendations.

In the text a number of previously dealt with subjects are taken up once again and examined in detail, for example those regarding the distinction of the various types of genetic tests, the legitimacy and possible limitations of

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[162] The document was drafted by the Joint Group, made up of the Italian Committee for Bioethics (ICB) and the National Committee for Biosafety, Biotechnology and Life Sciences (ICBBSV).

[163] Opinion edited by the Joint Group. A standardised format of a form for a flexible informed consent is attached (specific consent, partially limited, multi-option, broad), for the collection, preservation and use of cells and tissues in biological banks.

[164] This Opinion was also drafted by the Joint Group. The three Joint Group Opinions, along with three commentaries and Preface by Adriano Bompiani, have now been put together in a book by M. GALLETTI and M. TORALDO DI FRANCIA (edited by), *Bioetica e genetica. Indagini cliniche e biobanche tra etica, politica e società,* Franco Angeli, Roma 2013.

the right not to know, the risk that, beyond statements of principle, discriminatory and/or stigmatising behaviour can be manifested on the basis of assessments related to the individual genetic profile and instances of selection at work, school, etc. Nevertheless, the aim was to go beyond this and offer a broad reflection "*on the actual present, as well as prospective, value of the evolution of genetic research in the medical-healthcare field*" and on its related bioethical problems, focusing in particular on two interdependent sectors at the centre of a number of expectations. The first is that of the studies on the influences of hereditary traits in the most common multifactorial disorders (*"owing to the interaction between the additive effect of many genes and the environment"*), a sector which has given rise to the rapid proliferation on the market of the offer of predictive and susceptibility tests, of which the scientific validity is often not controlled, let alone the clinical one. Even then it was highlighted how the growing tendency to encourage the commercialisation of this typology of investigation without medical prescription and an adequate genetic counselling was a cause for great concern. Moreover, this took place by resorting to forms of misleading advertising and undue pressure on citizens-consumers, unaware of the dubious scientific and clinical validity of information to be obtained with this "freedom" of initiative, just as also the possible negative medical and non-medical consequences that could arise from this. The second sector of interest is in the research of pharmacogenetics and pharmacogenomics, which instead investigate the "*modalities of response to drugs at the level of the molecular structure of cells and tissues*" with the aim of developing tests to increase the efficacy of treatments and reduce the risk of adverse effects of a specific drug for a specific individual (the "*precision medicine*" – PM sector).

Instead, the second section addresses the role played by genetic counselling, along with an in-depth examination of the related bioethical issues – from those pertaining to informed consent to those of the protection of confidentiality and privacy and the relationship between the person undergoing the testing and their family etc. – also in view of the future growing development of clinical genetics and PM.

In this document the ICB had also foreseen that the rapid evolution of second generation genomic sequencing technologies (the so-called *Next*

Generation Sequencing, NGS) would have transformed and speeded up the research and diagnosis of many disorders; in the meantime these forecasts have for the most part materialised, to such an extent as to justify the affirmation of being before a real "*genomic tsunami*".

1. New genome sequencing technologies: WES and WGS

While in the past only single segments of DNA could be analysed, the new techniques make it possible to decrypt the whole exome (*Whole Exome Sequencing*, WES), or the whole set of exomes, about 1% of the genome, corresponding to the DNA transcribed into mature RNA, or even the whole genome (*Whole Genome Sequencing*, WGS), including a person's coding and non-coding sequences. All this can be done in time and with costs that are 1,000,000 times lower with respect to those necessary in 2000, when the first sequencing of the human genome was made public.

This progress has facilitated the access to genomic information and has brought about a significant increase in the use of new technology platforms both in clinical contexts (for example, diagnostics, pharmacogenetics, in screening) and in research. Commercial pressure then led numerous groups to propose the *Genome Wide Analysis* (GWA), or the analysis of specific portions of the genome, in the prediction of the individual susceptibility to getting a disease and various websites offer different genetic tests (susceptibility to common illnesses, personalised diet, ability in sports, choice of partner, etc.) directly to consumers (so-called "*Direct to consumer Genetic Testing*" - DCT)[165].

A fundamental feature of the ongoing technological revolution is the promise and, in some cases, the actual possibility of defining heritability (that is, the hereditary component), or part of the heritability of diseases and complex traits from a new perspective and, at the same time, to come closer to the objective of "personalising" medicine and therapies. The NGS techniques have ascertained that the genome of each person differs from those of others by almost 4 million base pairs (for the most part these are polymorphisms,

[165] On these aspects of DCT, see the Opinion by the Joint Group, *Genetic susceptibility testing and personalised medicine*, *op. cit*.

common genetic variations shared by at least 1% of the population, but often by many more) and has about 1500 "unique" bases, not present in the human genome reference maps. These variations are at the basis of inter-individual differences and give the foundation to the predictive tests, which measure the susceptibility and resistance of each person to common diseases.

The association between specific polymorphisms and diseases or complex traits, and hence their value in terms of susceptibility and impact on a certain phenotype, is established by means of the analysis of a great number of samples (thousands/tens of thousands) of subjects carrying a disease and unaffected controls. These studies make it possible to highlight the polymorphisms present in a significantly greater or smaller percentage of people affected, with respect to the controls, in support of a random association with the disease in question. As they are complex phenotypes, deriving from the additive effect of the genetically determined susceptibility and the environment, the predictive significance of the single polymorphisms is low (average additional risk 1.1-1.5). The 2,000 or more studies that have been carried out since 2005 on over 250 complex diseases/traits have made it possible to identify over 12,000 polymorphisms of susceptibility/resistance[166]. Nevertheless, apart from a few exceptions, the average hereditability decrypted for the single diseases is low and does not go over 15%. Furthermore, given that the frequency of polymorphisms in the various populations can be highly variable (with differences even in the range of 25%!), the transferal of research results in clinical practice should be very carefully considered insofar as the prediction of risks cannot disregard the knowledge of the frequency of the polymorphisms investigated in the population from which the person being offered the test originates[167].

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[166] D. WELTER, J. MACARTHUR, J. MORALES, T. BURDETT, P. HALL, H. JUNKINS, A. KLEMM, P. FLICEK, T. A. MANOLIO, L. HINDORFF, H. PARKINSON, *The NHGRI GWAS Catalog, a curated resource of SNP-trait associations,* "Nucleic Acids Research", January 2014, 42 (Database issue).

[167] T. A. MANOLIO, *Genomewide association studies and assessment of the risk of disease,* "The New England Journal of Medicine", July 8, 2010, 363 (2), pp. 166-176. The fact that the differences in the frequency of polymorphisms can depend on individual ethnic appurtenance is highlighted in many articles and documents, which stress how most of the known pathogenic mutations have been discovered in the Caucasian populations.

The impressive technological development and the consequent easy access to genomic analysis does not make it possible to make forecasts beyond a time span of 3-5 years, but justifies the question as to what the impact of large scale access to predictive tests will be.

With regard to the present we stress that:

a. at the moment it is premature to constructively use most of these results in a translational way and to offer an ad hoc genetic counselling. The biological bases of only a part of the genetic diseases are known and only a small part of the heritability of the complex ones; furthermore, the complex mechanisms whereby the environment modulates the action of the genome are only known in a piecemeal fashion.

b. the follow-up of the persons undergoing GWA with a DTC approach showed that the behaviour adopted following the giving of the test results is not significantly different from the behaviour that could have been adopted without undergoing a costly genomic investigation, insofar as choices oriented solely by common sense[168].

c. from the epistemological point of view, human genetics has modified its reference paradigms over the last years. It has in fact become clear that numerous products interpose between the genotype and phenotype, which share the "-omic" suffix, currently used to indicate a wide number of disciplines or biomolecular derivatives (including transcriptome, proteome, metabolome), which identify the different functional expressions of genes[169]. These products are not static but change significantly during life, in a different way in the various organs and apparatuses. Their totality defines the integrome, the ideally most appropriate parameter to describe the individual genomic or post-genomic profile[170].

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[168] D. J. KAUFMAN, J. M. BOLLINGER, R .L. DVOSKIN, J. A. SCOTT, *Risky business: risk perception and the use of medical services among customers of DTC personal genetic testing,* "The Journal of Genetic Counseling", June 21, 2012, (3), pp. 413-422*;* G. REMUZZI, *Così ho fatto la mappa del DNA e la mia vita è cambiata,* "Corriere della Sera", July 28, 2014.

[169] M. BAKER, *The omes puzzle,* "Nature", 2013, 494, pp. 416-419.

[170] R. CHEN, G. I. MIAS, J. LI-POOK-THAN, L. JIANG, H. Y. LAM, R. CHEN, E. MIRIAMI, K. J. KARCZEWSKI, M. HARIHARAN, F. E. DEWEY, Y. CHENG, M. J. CLARK, H. IM, L. HABEGGER, S. BALASUBRAMANIAN, M. O'HUALLACHAIN, J. T. DUDLEY, S. HILLENMEYER, R.

Moreover, today it is considered that these continuous changes are for the most part dependent on the individual exposome or, that is, on the lifestyles and the environment in which we develop, grow and live, including the trillions of bacteria present in our organism and, among these, in particular, the symbiotic microorganisms of the intestine (microbiota), which from birth play an important role in the modulation of the immune system of the host and the genome[171]. This not only means that a person cannot be defined uniquely on the basis of the genomic sequence inherited at the moment of conception (the old idea of genetic determinism), but also that post-genomic medicine is overtaking the traditional "reductionist" approach to move towards a holistic vision and one of "systems medicine", which in an interdisciplinary way looks at the human body as an integrated totality, which incorporates complex genomic interactions, both environmental and behavioural[172].

The convergence of systematic approaches to diseases – including the new diagnostic instruments and "omic" investigations, together with the new mathematical and computational tools – is destined to revolutionise the traditional paradigm of medicine with regard to the patient and in the next years to go on to develop a Preventive, Predictive, Personalised, Participatory medicine (the so-called "4P medicine")[173].

2. New questions: NGS and Incidental Findings – IF

The speed in the advance of technological development applied to the analysis of the human genome has raised a series of new questions of a

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HARAKSINGH, D. SHARON, G. EUSKIRCHEN, P. LACROUTE, K. BETTINGER, A. P. BOYLE, M. KASOWSKI, F. GRUBERT, S. SEKI, M. GARCIA, M. WHIRL-CARRILLO, M. GALLARDO, M. A. BLASCO, P. L. GREENBERG, P. SNYDER, T. E. KLEIN, R. B. ALTMAN, A. J. BUTTE, E. A. ASHLEY, M. GERSTEIN, K. C. NADEAU, H. TANG, M. SNYDER, *Personal omics profiling reveals dynamic molecular and medical phenotypes*, "Cell", 2012, 16, 148 (6), pp. 1293-1307.

[171] L. PUTIGNANI, F. DEL CHIERICO, A. PETRUCCA, P. VERNOCCHI, B. DALLAPICCOLA, *The human gut microbiota: a dynamic interplay with the host from birth to senescence settled during childhood*, "Pediatric Research", July 2014, 76 (1), pp. 2-10.

[172] T. KAMADA, *System biomedicine: a new paradigm in biomedical engineering*, "Frontiers of medical and biological engineering", 1992, 4 (1), pp. 1-2.

[173] L. HOOD, M. FLORES, *A personal view on systems medicine and the emergence of proactive P4 medicine: predictive, preventive, personalized and participatory*, "New Biotechnology", September 15, 2012, 29 (6), pp. 613-624; M. FLORES, G. GLUSMAN, K. BROGAARD, N. D. PRICE, L. HOOD, *P4 medicine: how systems medicine will transform the healthcare sector and society*, "Per Med.", 2013, 10 (6), pp. 565-576.

bioethical nature. In particular, with regard to the managing of genetic and genomic analyses, there has been wide debate on how to re-intervene on the existing normative frameworks regulating research and its clinical applications and it has been asked if and to what extent, it is appropriate to question a number of consolidated principles.

The need for new shared guidelines – at local, national and international levels – for the management of the challenges of this delicate stage of transition of the human genome is a strongly felt need also because the use of WES and WGS technologies, which generate a huge amount of data of potential clinical interest (which require complex bioinformatics analyses for their interpretation), weakens or even erases some traditional distinctions:

1) between research and clinical investigation, insofar as the two dimensions seem to be increasingly interwoven, and at the same time the problem of how to store and manage the growing amount of information that is becoming available[174];
2) between diagnostic tests and screening – understood as medical tests offered to asymptomatic persons and for whom there are no clinical indications such as to make them necessary – since the use of WES and WGS in the clinical context in principle generates a range of unforeseen information and/or uncorrelated with the original diagnostic query[175].

Whenever considering the great number of recommendations which have been drafted in recent years by the scientific organisations to regulate the management of NGS techniques, both in clinical applications and in research, it can be seen that in these documents the concern is always ex-

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[174] C. G. VAN EL, M. C. CORNEL, P. BORRY, R. J. HASTINGS, F. FELLMANN, S. V. HODGSON, H. C. HOWARD, A. CAMBON-THOMSEN, B. M. KNOPPERS, H. MEIJERS-HEIJBOER, H. SCHEFFER, L. TRANEBJAERG, W. DONDORP, G. M. De WERT, ESHG Public and Professional Policy Committee, *Whole-genome sequencing in health care. Recommendations of the European Society of Human Genetics,* "European Journal of Human Genetics", June 21, 2013, Suppl. 1: S1-5.

[175] B. M. KNOPPERS, *Introduction From the Right to Know to the Right Not to Know,* "The Journal of Law, Medicine & Ethics", Spring 2014, Special Issue: Symposium: The Right Not to Know, Vol. 42, pp. 6-10.

pressed of how to maximise the potential benefits and minimise the potential damage (in terms of false positives, the protection of confidentiality and privacy of information[176], etc.) respecting the dignity and autonomy of the people involved, but also – at least in many recommendations – their right to an open future, to the extent that is considered most appropriate by each of them. While the shared objective[177] is to speed up the progress of "precision medicine" and the development of the so-called "4P" medicine as far as possible, the risk feared by many is that a growing recourse to these methodologies in genetic diagnostics might lead to the automatic inclusion of patients in protocols of fact-finding studies, subordinating their individual interests to the research goals of their doctors. Thus, for example, the identification of a new variant of potential importance for the progress of scientific knowledge of a specific pathology, and therefore of great interest for research, could at the time be irrelevant for clinical ends; this would not only be difficult to explain to the patient, but could even be a cause of stress and anxiety to them and their family or also be responsible for provisions and inappropriate medical management[178]. Under this profile there seems to be widespread consensus on the need to proceed cautiously as far as concerns the introduction of the new genomic technologies into medical practice and on the rejection, in principle, of every simplistic application of the so-called "technological imperative" (everything must be offered that every technological advancement makes viable).

The hope mostly expressed by specialised literature is that an active exchange of experiences might be established between the geneticists that use WES and WGS, with clinical and/or research ends, in order to draw up shared rules that set down, case by case, the gradualness in the use of NGS techniques, as well as which genomic information can be extracted and when it must be documented, filed, shared and for how long. In parallel, there is

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[176] On the difficulties met by the protection of privacy in the age of NGS testing and "big data", see in particular S. S. SHRINGARPURE and C. D. BUSTAMANTE, *Privacy Risks from Genomic Data-Sharing Beacons.* "American Journal of Human Genetics", November 5, 2015, 97, pp. 1-18.

[177] On the announcement made by President Obama of huge financing for a new research initiative aimed at speeding up the progress towards the era of *precision-personalized medicine* see: F.S. COLLINS and H. VARMUS, *A New Initiative on Precision Medicine,* "The New England Journal of Medicine", February 2015, p. 26.

[178] C.G. VAN EL *et al.*, *op. cit.*

a hope for the construction of common normative frameworks that:

a. redefine the different stages and contents of genetic counselling in an appropriate manner for the new challenges together with the procedures for informed consent, differentiating research from clinical applications, and likewise for the management in both dimensions of the so-called 'incidental findings'- IF and the variants whose clinical implications are not yet certain (*variants of unknown significance* - VUS);

b. make it possible to come to a shared definition of what is meant by 'clinical utility', as a criterion legitimating the request for genetic testing or genomic analysis (definition on which there are a number of differing opinions).

With respect to point (b), the problem has long been debated, initially starting from the question of the guiding criteria to be applied in the offer of neonatal screening tests, to then also affect the guidelines for genetic and genomic analysis[179]. From this exchange of opinions a persistent contrast between two main concepts comes to the fore. One group considers that the classical criteria still hold and according to which the clinical utility of an investigation should be focalised on the identification of conditions for which efficient treatment or preventive measures aimed at reducing the morbidity and mortality are readily available. On the other hand, the other group proposes to extend its meaning, under the profile of the contents and interests to be taken into consideration. As far as the contents are concerned, the conditions are included that do not require immediate medical intervention, or for which efficient treatment is not available, or which are not clearly pathological. With regard to the possible benefits, the assessment is also extended to the interests of the family circle of the subject in question. In this second perspective, all the so-called "actionable"[180] information, or rather the information which prefigures the possibility of a decision-making inter-

[179] *Ibid.*

[180] G. M. CHRISTENHUSZ, *To tell or not to tell? A systematic review of ethical reflections on incidental findings arising in genetics contexts,* "European Journal of Human Genetics", 2013, 21, pp. 248-255.

vention on the part of the subject and their family (reproductive decisions, planning of life choices, insurance plans, etc.) come into the list of information of clinical utility and, consequently, to be communicated.

Looking more closely at the questions raised by the latest developments of genetic-genomic diagnostics, the debate has focused above all on the pros and cons in both research and clinical investigation of giving the persons directly concerned the so-called IF, that the WES and WGS inevitably generate and which can be important for health and/or for reproductive choices (the IF and VUS can moreover play a crucial role in the understanding of the genotype-phenotype correlations[181]), as well as on the exchange of reasons given in support of the different standpoints.

The *Presidential Commission for the Study of Bioethical Issues* of the United States, which had already in part dealt with the subject in the document "*Privacy and Progress in Whole Genome Sequencing*"[182] (with particular reference to wide scale genetic sequencing), dedicated its detailed report to IF "*Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts*"[183]. In this document the IF are defined as "results that are outside the original purpose for which a test or procedure was performed". The Commission divides the IF into "*anticipatable*" and "*unanticipatable*". The former are those in which the possible association with a test or procedure is known. The latter are the IF that cannot be foreseen on the basis of the knowledge at hand. Furthermore, the Commission distinguishes between "*primary*", "*secondary*" and "*discovery findings*". "*Primary findings*" refer to a result that is actively sought, using a test or procedure designed to find such result.

The "*secondary findings*" refer to the results that are actively sought by a professional, but which are not the "*primary target*". The "*discovery*

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[179] [181] See L. G. BIESECKER, *Incidental Variants Are Critical for Genomics,* "The American Journal of Human Genetics", May 2, 2013, 92, pp. 648-651.

[182] Presidential Commission for the Study of Bioethical Issues, *Privacy and Progress in Whole Genome Sequencing,* 2012, available from www.bioethics.gov/cms/sites/default/files/Privacy-and-Progress_PCSBI.pdf.

[183] Presidential Commission for the Study of Bioethical Issues, *Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts,* 2013.

findings" refer to the results of wide tests, aimed at detecting any potentially interesting data. The recommendations formulated by the Commission differ according to the IF category[184].

With respect to this aspect of the debate, while most agree in maintaining that all the IF of proven "clinical utility" must be communicated – meant in the sense of availability of treatment or efficient prevention measures – on the other hand opinions differ in specialist literature, discussion forums and in reviews, concerning the advisableness of communicating the IF of uncertain clinical significance (at the moment most of the IF), or those predictive of untreatable pathologies, or of the risk of a disease that is not quantifiable at individual level.

The different concepts also affect the way of thinking-rethinking genetic counselling, which must prepare patients, family and practitioners both to deal with more or less high levels of uncertainty and the processes and limitations of informed consent. In fact, not all of them are in favour of leaving patients enrolled in a research study, or who need a genomic investigation, more than one option to know/not know the IF discovered during the investigation (for example, no knowledge; qualified knowledge, or only the information of clinical interest liable to intervention, including or not including the information important for reproduction choices; knowledge of the variants of uncertain clinical significance, etc.). In reality, there are thus considerable differences regarding the identification of the most suitable modalities to protect patients and subjects enrolled in studies.

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[184] Even though recognising that the expression "Incidental Finding" is not always the most appropriate, the ICB continues to use it in this document because it is used internationally. For example: J. K. HEHIR-KWA, M. CLAUSTRES, R. HASTINGS, C. VAN RAVENSWAAIJ-ARTS, G. CHRISTENHUSZ, M. GENUARDI, B. MELEGH, A. CAMBON-THOMSEN, P. PATSALIS VERMEESCH, M. C. CORNEL, B. SEARLE, A. PALOTIE, E. CAPOLUONGO, B. PETERLIN, X. ESTIVILL and P. N. ROBINSON, Meeting Report, *Towards a European consensus for reporting incidental findings during clinical NGS testing*, "European Journal of Human Genetics", 2015, 23, pp. 1601–1606; Hellenic National Bioethics Commission, *Incidental Findings in Research and Clinical Practice,* 26 June 2015. In the Meeting Report it is stressed that the use of the expression *incidental findings* includes (i) unexpected positive findings, but also (ii) the intentional search for pathogenic variants not associated with the primary diagnostic query. Nevertheless, it is considered that the use of a different term, for example, "unexpected" or "secondary" or "unsolicited" findings, is just as problematic and therefore it is advised to keep to the most common use of "*incidental findings*".

Even considering the European context alone, with regard to the use of NGS techniques in clinical diagnosis, a general agreement has not yet been reached on the question of documentation, reporting and communication of IF and the unclassified variants; more specifically: on the rules that genetic diagnosis laboratories should adopt, the modalities of storage-filing-sharing of the data produced from these analyses with other laboratories and on the actual possibility of their future re-interrogation[185]. As far as the research is concerned, the debate is made even more complex by the scepticism of many researchers about the concrete possibility of guaranteeing a return of information to those who donate biological samples, progressively as new data are made available on genetic variants that are potentially important for health. The vast amount of data generated and the possible, or probable, loss of contact with the original donors in fact seems to make the respect for the "right" to be informed hardly realistic, should there be an explicit request, unless new modalities to maintain relations and communication by websites, social forum etc. are identified.

Given the rapid progress of genetic and genomic research, even the *International Bioethics Committee (IBC)* of UNESCO[186] felt the need to update the previous documents on the genome and human rights, elaborating its new considerations in which the ethical issues deriving from the most recent advances, both in genetic diagnostics and the emerging gene-editing techniques, are listed and tackled. In the latter document, the IBC wishes to highlight how at present it is the very lack of a widespread ethical sensitivity, together with the inexistence of a framework of shared rules at the international level, that risks producing harmful effects in terms of protection of fundamental human rights, increasingly marked inequalities in life and health expectations, new dangers of discrimination and/or stigmatisation of persons and/or specific groups.

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[185] See Meeting Report, *Towards a European consensus, op. cit*.

[186] UNESCO – International Bioethics Committee, *Report of the IBC on Updating Its Reflection on the Human Genome and Human Rights*, 2 October 2015.

a) Aspects of the bioethical debate on IF

A catalysing role of the debate on some of the above mentioned subjects was carried out by the publication of the *Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing*, drafted in 2013 by the *Working Group* of the *American College of Medical Genetics and Genomics (ACMG)*[187], which questioned the guidelines on the offer of genetic testing in medicine. According to the authors, in the age of the "*genome wide*" (GWA) analysis, many old rules and distinctions would no longer have any justification, as they are just a hindrance to the development of knowledge and a restraint to the translational use of new acquisitions. With regard to this, the *Recommendations* identify three main critical targets:

1) First of all, the thesis of the non-comparability of genetic information to other clinical data is rejected, or the thesis of the so-called genetic "exceptionalism", conferring to this category of personal information a special legal status and a particular safeguard in terms of *privacy*[188]. According to the Working group, when a genomic analysis is carried out an attempt should be made to communicate all the information of potential clinical interest, whether correlated or not to the primary diagnostic question, just as happens when, for example, a patient complains of symptoms in the digestive system, the doctor does not just examine that system but extends the examination to the heart and lungs to try and find the evidence of a complex illness, or to discover other symptoms of the disease.

2) Secondly - "genetic exceptionalism" having been rejected – the subjects who undergo a WGA, upon specific medical advice, are denied the possibility to exercise the 'right' to not know some secondary results (IF),

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[187] R. C. GREEN, J. S. BERG and W. W. GRODY *et al.* for the American College of Medical Genetics and Genomics, *Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing,* "Genetics in Medicine", 2013, 15, no. 7, pp. 565-574.

[188] Genetic "exceptionalism", recognised by many supranational documents, and not without contestations, is justified on the basis of the peculiar nature of these "very sensitive" data, (i) which are structurally shared with other subjects belonging to the same biological group and (ii) that "*make it possible to know in advance a number of aspects concerning one's biological future, in terms whether it be of greater susceptibility with respect to the average, to having certain diseases (or also resistance to the same), or predestination to getting a certain disorder or an early death*", see Opinion by the Joint Group, *Genetic testing and insurance, op. cit.*

independently of their preferences and clinical condition. The drafters of the document recognise that this recommendation is in conflict with the ethical and juridical norms that safeguard the patient's autonomy, but consider that the doctors and laboratory staff, have a more cogent "fiduciary" duty, which is one of preventing any potential harm (principle of beneficence) and, for this reason, to always give patients the IF of potential interest for their health, even against their will.

3) Thirdly, in relation to the rules to be applied in the carrying out of genomic analyses, the distinction between minors and adults is rejected. In stressing the need to always communicate the IF, at least concerning the analysis of a given group of genes, even if they are predictive of genetic diseases with late-onset and incurable and/or preventable, the Working Group maintains that this rule should hold also in case where the investigation concerns new born babies, children or adolescents. Once again it can be seen that a similar indication is in clear contrast with the most accredited guidelines on the subject, which recommend not to subject minors to predictive genetic testing at the outset of adult life, which are neither preventable nor sensitive to efficacious treatment. This recommendation is defended with the justification that, in the balance between the possible benefit for the parents deriving from the knowledge of their genetic risk and the potential harm that could be done to the minor with the questioning of their future autonomy and right to an open future, at present the first aspect prevails over the second.

In short, the ACMG Working group recommends that, when a WGA is prescribed with a specific clinical suspicion, a series of conditions/genes/variants are always analysed (the Table attached to the recommendations lists 56 genes associated with the risk of various diseases; this list is subject to yearly updating); the positive tests must then be communicated to the doctor prescribing the testing and he or she in turn must inform the patient, without leaving him or her the faculty to opt for non-knowledge of the results not correlated to the primary clinical suspicion or to opt to know only some. Despite admitting the lack of significant data on the clinical utility of these recommendations, the drafters support their fairness, relying on the argument of the future advantages to be derived from the acquisition of new knowledge, through the gathering of empirical data

on the penetrance of a series of variants of interest, as well as evidence useful for improving the analysis of the cost/benefit relationship.

Besides the acceptability or not of the tests carried out, these recommendations have had the merit of stimulating a huge structured debate on the ethical legitimation of the "right not to know" in a genetic context, during which misunderstandings and misinterpretations arose which have always existed in the bioethical debate on this controversial right and its possible theoretical foundations. The same ACMG *Board of Directors*, following a broad consultation of its members on the opinions, was led to review its own standpoints, recognising patients who undergo WES or GWA the possibility, during the pre-test phase of the counselling, to allow or not allow the extension of the investigation to the genes included on the list not correlated to the original diagnostic suspicion (excluding the option to choose only a subgroup of clinically "actionable" genes)[189].

b) Conceptual misinterpretations: "self-determination", "autonomy", "*privacy*"

In this clarification process, an important part was played by the Symposium *From the Right to Know to the Right not to Know*[190], held in Canada in the spring of 2014 – with the participation of numerous scientists, jurists and moral philosophers – who contributed to clarifying the assumptions of the right not to know from a conceptual point of view. The discussion during the Symposium and what followed on from it was focussed on three main issues:

i. the first, the more theoretical one, concerns the legitimation modalities of the "right" to Not receive personal information regarding one's health, genetic-genomic information included. It soon became apparent how the diverging ethical-philosophical interpretations of the concept of 'auton-

[189] See American College of Medical and Genomics, *Updates Recommendation on "Opt Out" for Genome Sequencing Return of Results*, Bethesda, April 1, 2014, available from www.acmgfoundation.org

[190] *From the Right to Know to the Right Not to Know,* "Journal of Law, Medicine & Ethics", *op. cit.*, pp. 1-6.

omy' lead to basing arguments both in favour and against the recognition of the "moral" right not to know (RNTK) on contrasting ethical and juridical principles.

ii. the second question regards the possibility or not of envisaging a moral duty to undergo tests, when it is presumed that they may be relevant not only for one's life choices, reproductive ones included, but also those of one's blood relatives. With its evident sociological implications this second profile of the debate contributed to defining, not without differing opinions and more or less knowingly, a new figure of "ideal citizen": an autonomous, careful, responsible subject, who formulates his or her own life strategy in a calculated way, with choices that look to the future in terms of optimisation of management of their own biological "risk" and that of their next of kin, availing of biomedical knowledge, as a resource for the planning of their existence[191].

iii. the third query concerns researchers and their possible obligation to guarantee, also for the future, a return of information of clinical utility to the participants enrolled in genetic and genomic testing.

While the debate is still ongoing on points (ii.) and (iii.), as far as concerns point (i.) a number of important conceptual clarifications have been made, which should be briefly summarised insofar as useful to outline more precisely what is at stake in the bioethical debate on IF.

It must be first of all recalled that until 1977 the supranational and international documents of normative importance did not mention the possibility of guaranteeing a right not to know in healthcare, insofar as the emphasis had moved to the individual right to be informed. Only in 1997

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[191] See N. ROSE, *The Politics of Life Itself. Biomedicine, Power and Subjectivity in the Twenty-First Century*, Princeton University Press, Princeton 2007. Also the last UNESCO document on the subject highlights how the possibility to know one's own genomic make up can give rise to the social expectation that persons plan and live their lives in accordance with this knowledge. This expectation could not only make people lose sight of the importance for health of the many social determinants affecting it, but also lead to discriminate and stigmatise those who do not adopt "*a health-promoting lifestyle*"; see *Report of the IBC on Updating Its Reflection on the Human Genome and Human Rights, op. cit.*

did the RNTK, characterised as an aspect of personal autonomy, find its first formal recognition – which was followed by many more in the *Universal Declaration on the Human Genome and Human Rights* UNESCO (art.5) and, in the same year, in the *Oviedo Convention on Human Rights and Biomedicine* (art.10). Nevertheless, the question of the plausibility of the RNTK in the bioethical debate has continued to be a controversial matter, owing to the persistent lack of agreement on the ethical-philosophical meaning of the concept of "autonomy" and the ensuing rights and/or interests to be safeguarded[192].

There are three main interpretations of this concept, which in turn envisage different ideals of what can be meant by "autonomous decision" and different, sometimes conflicting, approaches to their normative importance.

For the first ideal, what has value and is worthy of protection, is the non-interference by others in the most personal and inmost decisions. In this case autonomy coincides with the personal liberty of the competent adult subject to decide on their own life and, therefore, requires a policy that might guarantee the corresponding rights, including that of refusing to receive information on one's own health.

The second much more demanding interpretation interprets the concept as an ideal that requires the competent subject, insofar as moral agent, to be in control of the circumstances of their own existence. For this concept people have the right and duty to know as much information as possible about their own state of health, genetic make-up included, to be able to exercise "self-governance" taking rationally controlled decisions[193], or that is, based on all the relevant information that can be obtained. This excludes the possibility *a priori* of morally establishing the claim to remain in ignorance.

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[192] In particular see the essays by: G. LAURIE, *Recognizing the Right Not to Know: Conceptual, Professional, and Legal Implications*, *op. cit.*, pp. 53-63; G. HELGESSON, *Autonomy, the Right Not to Know, and the Right to Know Personal Research Results: What Rights Are There, and Who Should Decide about Exceptions?* in *From the Right to Know to the Right Not to Know, op. cit.*

[193] J. HARRIS and K. KEYWOOD, *Ignorance, Information and Autonomy,* "Theoretical Medicine", 2001, 22, 5, pp. 415-436.

A third concept of the notion, often disregarded and opposed to the previously mentioned one, instead connects autonomy to an ideal of "authenticity". From a philosophical perspective, this standpoint found its most respected supporter in the 70s in the person of Hans Jonas. With the rapid advance in biomedical technologies which seemed to question the "*right to every human life to find its own way and to be a surprise for itself*", Jonas had already envisaged the emergence of a new moral right, that is, a right to the ignorance of one's own future, which in certain situations (for example, in the case of predictive information on late-onset non-preventable and untreatable genetic diseases), can be presented as a precondition of the free construction and definition of self-identity.[194]

While the second interpretation is incompatible with the recognition of the RNTK, instead for the other two such right finds a foundation, at least as a "prima facie" right (or liable to exceptions in particular circumstances), in the one case in the negative freedom of the person and in the other in the 'existential' freedom of self-determination according to one's values and lifetime plans.

Nevertheless, if one passes from the philosophical-moral level to the factual one of the concrete dilemmas that doctors and doctor-researchers can be faced with when they find themselves before IF, the above mentioned do not help to resolve the question of the decision to be taken should an explicit expression of will by those directly concerned be lacking to be or not be informed.[195] In these cases some consider that a reconceptualization of the interest to not know is more suitable as a question deriving from the interest in the respect for privacy[196], understood as "separateness" of the "private" personal sphere – including the very individual psyche - not accessible to others if not for good reasons. In this perspective, it can therefore be maintained that the communication of unsolicited personal information, regarding one's own genetic makeup can constitute, more than a violation of autonomy, an invasion of the individual psychic sphere.

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[194] On the concept of the "free formation of self" in relation to the "right to ignorance", see the Joint Group, *Genetic testing and insurance, op. cit.*, and *Genetic susceptibility testing and personalised medicine, op. cit*.

[195] For example in the case of a diagnosis made with NGS on a biological sample of a dead subject and whose result can, nonetheless, have clinical relevance for blood relatives.

[196] See G. LAURIE, *Recognizing the Right Not to Know: Conceptual, Professional and Legal Implications, op. cit*.

In conclusion, it can be said that the interest and/or right not to know must be safeguarded as much as possible, even though it is never absolute insofar as it can come across limitations, in factual circumstances, for reasons that surpass it and which must therefore be convincingly argued each time. A certain degree of discretion can never be completely avoided since it ultimately lies with the responsibility of the doctors and doctor-researchers, with the help of other consultants, to decide on the "exceptions", bearing in mind the relevance of the typology of information at stake.

Recommendations

Even though aware that this transition from basic knowledge to clinical applications is characterised by a high level of uncertainty and knowledge that risk being surpassed very rapidly, the ICB has formulated a number of recommendations.

1) For the tests based on NGS, the ICB recommends that:

i. the analysis is carried out only in accredited genetic diagnosis laboratories, which are subject to external quality control, perform an adequate number of analyses, are equipped with updated databases and IT instruments, able to guarantee the accuracy of the diagnoses and the interpretation of the results, and an organisation for the storing of all the data generated, including incidental findings (IF) and variants the clinical implications of which are not yet certain VUS – Variants of Uncertain Significance - considered time-dependent). The ICB expresses its hope that standard criteria might be shared and valid over all the national territory;

ii. the genetic centres share operational rules for the choice of molecular diagnosis techniques, which must be calibrated bearing in mind the specificity of the primary diagnostic query and the analysis of the variants identified. Should the WES analysis be negative, the centres must take the necessary measures for the preservation of the biological sample and the patient's data, so as to make them available for possible further analyses once new knowledge and data has been acquired;

iii. more room is reserved for the gathering of informed consent and pre- and post-test counselling, which must be an integral part of the analysis and be carried out by professionals with specific training, including psychological training[197];

iv. the patients undergoing counselling are informed preliminarily, in the pre-test genetic consultation, of the potential and the limitations of the analysis and the differences with respect to traditional tests, particularly with regard to the possibility of the analysis identifying IF of possible clinical outcome and VUS, as well as information on the possible biological blood relationships and information of pharmacogenetics interest and precision medicine. With regard to this and in line with what was proposed in a recent document of the Italian Society of Human Genetics (SIGU)[198], the ICB considers it useful for the patients undergoing consultation to be shown a number of significant examples of conditions whereby IF are more likely to be highlighted. Those undergoing testing must moreover be informed that the results of the analysis can have serious implications for their next of kin and that, in this case, it is appropriate and in some circumstances dutiful[199], to allow the latter to be informed with due caution and modalities;

v. in the obtaining of informed consent, the patient's right to self-determination be respected and therefore the choice to decide which results to know be left with the patient undergoing testing, once they have understood the difference between the various typologies of IF. The patient must be free to choose whether to refuse information on IF or to receive only the information relative to preventable or treatable pathologies, or again to also

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[197] See the paragraphs dedicated to outlining the modalities and contents of genetic consultation in the opinion by the Joint Group, *Test genetici di suscettibilità e medicina personalizzata*, *op. cit.*

[198] SIGU-NGS Commission, *Il sequenziamento del DNA di nuova generazione: indicazioni per l'impiego clinico*, 2016, including attachments: *Indicazioni operative per la consulenza genetica associata ai test NGS, Informativa al consenso. Test genetico: "sequenziamento dell'esoma"; Foglio Informativo per l'analisi di regioni selezionate; Consenso Informato per Analisi di regioni selezionate; Schema risposta indagine NGS.* In this document it is specified that, in clinical diagnostics at the present time, WGS analysis is not considered, owing to the high cost and difficulties of interpretation.

[199] For example, in the case of information on serious diseases for which it is necessary to start preventive or therapeutic measures.

know the data regarding pathological conditions that at that moment are neither preventable nor treatable[200]. In the pre-test counselling it is necessary to inform patients that in some cases the results of the tests may need further detailed examinations, for which the analysis of other members of the family might be required, to make it possible to study the 'segregation' of the variants identified[201]. Lastly it is necessary to ask the patient for a specific consent to be contacted in the future, should the need arise to do so;

vi. a relationship of collaboration and exchange of information be established between the laboratory, the geneticist and the other consultants having charge of the patient and that at the same time the collaboration is encouraged between the various diagnostic laboratories and genomic research. It lies with the geneticist who prescribed the testing to give the result, as he or she is acquainted with the patient's medical and family history, as well as with the choices taken down in the informed consent; in the post-test counselling he or she will be able to avail of the support of other professional figures, with psychological expertise too, who will help in the communication and planning of the patient's clinical management.

2) The ICB reiterates that the undefined demarcation of the boundary between research and its clinical applications must never make the geneticists and the other professionals lose sight of the fact that the diagnostic tests have the primary aim to give a diagnosis of the patient, whose needs must remain at the centre of the investigation; it therefore recommends that the patient/sample is included in a research project only after the course of diagnostic investigation has been concluded (either positively or negatively).

3) Furthermore, the ICB recommends that the traditional distinction between adults and minors be maintained in medicine and research alike, and that the "best interest" of the subject not yet able to give their own consent should be particularly and carefully evaluated. For these cases

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[200] On the other hand, it is not appropriate to give the variants of uncertain significance, nor the susceptibility for the above mentioned reasons.

[201] SIGU-NGS Commission, *Il sequenziamento del DNA di nuova generazione, op. cit*.

it hopes that the genetic centres have specific standard rules, both for the modalities through which genetic counselling is carried out and for the communication of results (only those of proven clinical utility) to parents/legal representatives. It is also recommended that, upon coming of age, the minor is contacted once again and can chose whether to give/not give their consent to further preservation of their samples and data[202].

4) Regarding the question of the returning of information of biological samples for research to donors, the ICB considers that, in the case of research that foresees the gathering of large numbers of samples, it is unrealistic to contact the donors to update them on the results, which moreover, to date, would hardly have any clinical significance of individual interest. Therefore the ICB recommends that it is always specified in the informed consent form whether or not this possibility exists and, should it be so, that the choice of information that they desire to receive be left to the person concerned.

5) On the other hand, the ICB considers that if requested it is morally dutiful to guarantee the return of the results of clinical importance (IF included) to the patients with rare diseases which are still without a certain diagnosis, who are part of study protocols and who donate their samples in the hope of advancing the knowledge of the causes of their illness, and thus recommends that this guarantee be maintained, always leaving the person concerned the possibility to opt to know only some types of information.

6) Lastly, the ICB stresses that the central role assumed by genetics and genomics in the healthcare panorama makes it increasingly urgent to rethink the training of professional figures working in healthcare together with the organisation, at various institutional levels (starting from school) of initiatives aimed at citizens, in order to promote the gaining of the necessary knowledge, including bioethical knowledge, to actively and crit-

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[202] The subject has already been dealt with by the ICB in the Opinion on *Paediatric biobanks*, *op. cit.*, April 11, 2014

ically tackle these transformations. In this sense the institutions must set up interventions aimed at countering misleading publicity, so that citizens are not the victims of the illusory and potentially harmful promises of many websites offering genetic and genomic testing directly to consumers.

Glossary

ACMG, *American College of Medical Genetics.*
Genetic counselling – A health service that provides information on genetic disorders relatively to their diagnosis, how the condition is inherited, the risks of occurrence or recurrence and the options for their control and prevention.
Person undergoing counselling – Person who receives genetic counselling
Pre-symptomatic diagnosis – Investigations aimed at ascertaining whether a person has inherited a gene-disorder before it is clinically manifested.
DTC, *Direct to consumer Genetic Testing - G*enetic testing refers to testing sold directly to consumers usually via private laboratories.
Hereditability – The hereditary component of a complex trait.
ESHG, *European Society of Human Genetics.*
Exome – Part of the genome formed by exons which represent the codifying portion of DNA. Even though constituting only 1% of the total amount of genetic material, it is made up of over 30 megabases (30 million bases) of DNA and is responsible for the building of our organism.
Expression – Variation in the degree of manifestation of a phenotype of a particular gene
Exposome - Totality of environmental factors to which an individual is exposed, lifestyle included.
Late onset age – Defines some phenotypes not present at birth, which are manifested in adulthood.
Phenotype – The appearance (physical, biochemical and physiological) of a person, which is influenced by the interaction of the genotype with the environment.
Gene Editing – gene or genome editing, which uses engineered nucleases, is a type of genetic engineering in which DNA is inserted, deleted or replaced in the genome of an organism using engineered nucleases, or "molecular scissors".
Genotype – Genetic makeup of a person.
GWA, *Genome Wide Analysis* – Analysis of the whole genome.
IBC**,** *International Bioethics Committee (IBC)* of the UNESCO.
IF, *Incidental findings* – Term applied in the case of genetic or genomic

analyses to mutations or variations that can have clinical implications, but which are discovered unintentionally during tests being performed for an unrelated medical condition. Not all these findings can be interpreted at the time and can have an uncertain meaning.

Integrome – Totality of all the integrated "omes" (genome, transcriptome, proteome, metabolome, etc.).

P4 medicine – Definition proposed by Hood and Friend as an acronym of Preventive, Predictive, Personalized, Participatory.

Systems medicine - An interdisciplinary field of medicine that analyses the systems of the human body as part of an integrated whole, incorporating genetic, biochemical, physiological, and environmental interactions.

Precision medicine – A medical model that proposes the customization of healthcare, with medical decisions, practices, and/or products being tailored to the individual patient. It is often used as a synonym for personalised medicine.

Metabolome – Totality of the **metabolites** of a biological organism, that is, of all the substances that can take part in the processes of an organism.

Monofactorial (**monogenic**) – Trait regulated by only one gene.

NGS, *Next Generation Sequencing* – Second generation sequencing, new genomic analysis techniques.

Genetic polymorphism – Common genetic variation, occurring in at least 1% of the population.

Proteome – Entire set of **proteins** of an organism or a biological system, or the proteins produced by the **genome**

Screening – Identification of persons with a disease or who are carriers of the gene of a disorder in a population.

Segregation (analysis of) – Study of the modalities whereby a disease or trait is transmitted in a family, in order to establish an inheritance model.

SIGU, Società Italiana di Genetica Umana – Italian Society of Human Genetics

Predictive test – It measures the susceptibility or resistance of a person to a disease (usually with late onset), that is different from the average general population.

Pre-symptomatic test - It finds out whether a person has inherited a genetic disorder before it becomes clinically evident (this includes also 'late onset' genetic disorders)

Transcriptome – Total set of transcripts (RNA messengers or mRNA) in a given organism, or cell type.
VUS, *Variant of Uncertain Significance* – A type of *incidental findings*, to which at that moment a certain significance (normal or pathological) can be given.
WES, *Whole Exome Sequencing* – Sequencing of the exome, corresponding to about 1% of the genome where the codifying genomes are to be found.
WGS, *Whole Genome Sequencing* – Sequencing of the entire genome.

Presidenza del Consiglio dei Ministri

COMITATO NAZIONALE
PER LA BIOETICA

MOTION

PAID SURROGACY

18 March 2016

The ICB has spoken out repeatedly against the commodification of the human body (Motion on the trade of organs for the transplant, 18 June 2004; Motion on the trade of ovocites,13 July 2007; Opinion on Illegal trafficking of human organs from living donors, approved on 23 May 2013).

In these documents the ICB recalled and endorsed the provisions of art. 21 of the Oviedo Convention on Human Rights and Biomedicine (1997): "The human body and its parts shall not, as such, give rise to financial gain", providing, as reaffirmed by art.3 of the European Charter of Fundamental Rights (2000), that it constitutes one of the ethical principles of the European Union.

The ICB points out that surrogacy is a contract which damages the dignity of the woman and the child, who, like an object, is subjected to a deed of sale.

The ICB believes that this hypothesis of commercialization and exploitation of the female body in its reproductive capacity, under any form of payment, explicit or surreptitious, is clearly contrary to fundamental bioethical principles also arising from the documents mentioned above.

The Committee intends to address the issue of surrogacy rendered without any financial reward in a specific more detailed opinion.

** ** **

The text, discussed in the plenary session of 18 March 2016, was voted and approved by those present: Profs. Salvatore Amato, Luisella Battaglia, Carlo Caltagirone, Stefano Canestrari, Francesco D'Agostino, Antonio Da Re, Lorenzo d'Avack, Mario De Curtis, Dr. Riccardo Di Segni, Profs. Paola Frati, Silvio Garattini, Marianna Gensabella, Assunta Morresi, Andrea Nicolussi, Massimo Sargiacomo, Lucetta Scaraffia, Monica Toraldo Di Francia.

Profs. Carlo Flamigni, Demetrio Neri and Grazia Zuffa voted against.

Dr. Maurizio Benato, Dr. Carla Bernasconi, Prof. Anna Teresa Palamara and Dr. Carlo Petrini members without the right to vote also acceded.

Profs. Carlo Casonato, Bruno Dallapiccola, Laura Palazzani, Rodolfo Proietti and Dott.ssa Rosaria Conte, members without the right to vote, who were absent from the session, subsequently gave their approval.

Prof. Cinzia Caporale, absent from the meeting, later expressed her disapproval.

Prof. Carlo Flamigni sent a dissenting codicil and Profs. Cinzia Capo-

rale, Demetrio Neri and Grazia Zuffa sent a statement of dissent. Both Notes are set out below.

Motion on the so-called womb for rent approved by the majority on March 18 – A Note of dissent by Prof. Carlo Flamigni

Before this motion (in its first version, which condemned all forms of "substitute motherhood" was discussed and voted on at the plenary meeting on Friday 18 March, I had presented a lengthy document in which I asked to differentiate between the various forms of surrogacy (to distinguish between, to use the media definition, womb for rent and the gift of the womb) and I put forward the question of setting priorities, recommending that evaluation be given in regards to the appropriacy of urgently considering an issue of scarce numerical significance as that of "surrogate motherhood", while ignoring issues such as prostitution, the trafficking of young girls and pedophilia. In fact I had been struck very disagreeably by a statement issued by the Minister of Health (February 4, 2016) according to which "surrogate motherhood" is one of the worst forms of prostitution, an insult that, neither the women who are its protagonists nor their children (inevitably the "sons of whores"), deserve. My document was not taken into consideration and, being rather long and not having found a place here, it will be on my website (www.carloflamigni.it) in April-May. Here I will only consider the issue of the so-called "womb for rent", and, as in the last plenary meeting of the Committee, the one in which this motion was passed, I was accused of being a man (indeed, a gynaecologist) and therefore understanding so very little of the mysteries of the feminine soul, I will try to make good use of my recent collaboration with a brilliant young researcher at the University of Bologna, Angela Balzano (how we came to shared conclusions can be understood by reading a book we wrote together Sexuality and Reproduction, published by Ananke in 2015) and an essay by M. Cooper and C. Waldby (Biolavoro Globale, DeriveApprodi 2015) that Angela translated and which also contains two of our documents.

Like the ICB, I too have repeatedly declared myself against the commodification of the human body, in all its forms. If, therefore, I do not point my finger against "substitute motherhood" (it would be better to call it "gestation for others" or "gift of the womb") it is because I see it as a potential

tool for self-determination, not only for parents who commission it, but also for the women who voluntarily agree to this gift, or sale, of their generating capacity, which means that the main thing that has to be discussed concerns the right to manage one's own body and the lawfulness or the convenience of placing limits even in those cases where it is absolutely respectful of the rights of others and does not produce any kind of damage whatsoever. It is best to immediately point out that a hypothesis emerged out of the discussion that took place within the ICB according to which this "gift" does not actually exist, what there is, is only an exchange, a hypothesis I knew very little about, and that I have always considered something in between an excusatio non petita and hypocritical self-criticism of capitalism.

I do not invoke strict regulatory requirements, nor do I side with campaigns claiming international prohibitions, rather I limit myself to trying to understand why today there is so much talk about substitute motherhood, and why there is the tendency to present it as an emblem of every form of commercialization of the living. Perhaps reasoning would be based differently if, in addition to keeping in mind international regulations, attention was paid to some real data. Certainly the use of new techniques of "total surrogacy" has increased in recent years but the numbers of couples and persons accessing it remains very small, both in absolute terms, and if compared to that of those who engage in the more traditional therapies of assisted fertilization with third-party gametes. For instance, let's take a look at what happens in the United States: according to the statistics of the Centers for Disease Control on examination of the figures for 2008, "surrogacy" was used in only 1% of medically assisted procreation cycles (slightly over 900 times), while the oocytes harvested from third party women were used in approximately 12% of the cycles, enabling the birth of 5,894 children[203]. We do not know how many people in Europe have resorted to surrogacy because there are no formal documented numbers (in countries where "surrogacy" is forbidden, those who use it may be prosecuted, which certainly does not help with the collection of data), but in any case we are talking about very low numbers compared to those related to MAP. It is worth mentioning the

[203] Centers for Disease Control and Prevention, 2008 Assisted Reproductive Technology Success Rates. National Summary and Fertility Clinic Reports, Department of Health and Human Services, Atlanta: US 2010.

Observatory study on procreative tourism, which shows that in 2011 the number of Italian couples who went abroad for "Surrogacy" were 32, against 4000 emigrating to obtain "heterologous" fertilization.

To begin, I thought it appropriate to choose well known ground; more than ten years of prohibiting fertilization with the gametes of others has shown that the choice of regulations dripping with bans and prohibitions on reproduction has as its sole outcome to create substantial differences based on census, with the more affluent being widely favoured and the poor forced to seek their fortune in laboratories and centres that are as inexpensive as they are unreliable. According to a recent study published by Human Reproduction[204], Italy is the European country that contributes most to swelling the queues of procreative tourism: out of 46 centres for MAP, and 1,230 couples, 392 were Italian. In a year about ten thousand Italian couples cross borders to find the gametes necessary for MAP, and these figures relate to only one month of monitoring. In the seven countries examined (as well as Italy, the figures refer to Spain, Switzerland, Belgium, Slovenia, Czech Republic and Denmark), Italian couples accounted for 31.8% of the total, a number that shows no sign of decreasing even after our Constitutional Court declared illegal the ban on donation of gametes and embryos. In regards to this, I include the testimony of Elizabeth Coccia, former president of CECOS, who explains that Italian state centres are signing agreements with foreign gamete banks: "Some clinics, at least 12, have already finalized contracts, and with the "foreign" gametes already having arrived a first confirmed pregnancy has been obtained. Even the Careggi hospital in Florence, one of the few state run centres where heterologous fertilization started off, has just finalized four contracts with European banks, two Spanish and two in Northern Europe, after having issued a public call for interest notice to which several certified European centres replied [...]. The decision to make agreements with foreign countries remains at the moment, the only possible way to guarantee heterologous fertilization in our country."[205] Logic suggests, therefore, that banning surrogacy in Italy does not decrease recourse to the technique, but only determines an increase in reproductive tourism, increasingly resulting in regulating access to it according to

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[204] F. SHENFIELD *et al.*, *Cross border reproductive care in six European countries*, "Human Reproduction", 2010, 25/6, pp. 1361-1368.

[205] Available at www.ansa.it/saluteebenessere/notizie/rubriche/salute.

income. There are already destinations for citizens of the upper classes, such as California, and destinations for the middle classes (and it looks like the perfect place for these treatments is once again India).

Too often our moral ideals move us away from the desires of real people and prevent us from feeling compassion for their suffering. I have encountered many men and women whose only desire was to have a child that they recognized as their "own" from a biological point of view. We may personally have never felt this desire, but a lack of empathy is not a valid reason to prevent the realization of the desire of others, at least in the context of the law. If gestation for others is not a practice that causes damage to third parties then there is no reason to ban it. Since many people claim that there is in fact an injured party, that of the surrogate mother, I invite you to explore the blogs that exist, that are managed directly by the " substitute mothers" of North America, who declare "I love to be pregnant" and justify their choice stating: "surrogacy is one of the most beautiful gifts we have to give"[206].

In addition, a study conducted in 2005, which compared twenty-seven empirical studies, reports that in North America "gestational surrogate mothers" are "twenty or thirty- year olds, white, Christian, and married with children of their own" and that "family incomes of the surrogate mothers are often very modest (but not extremely low), since they are predominantly women who belong to the working class"[207] (in which case the hypothesis of non-existence of the "gift" really seems nonsense to me). I know that the situation is different in India, where women who become "substitute mothers" have lower incomes; from ethnographic studies by Kalindi Vora[208] and Amrita Pande[209], it is evident that the "surrogate mothers" are mainly agricultural day workers, housewives who do cutting and sewing work from

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[206] See: among others, the blog http://www.scarymommy.com/5-things-say-gestational-surrogate/.

[207] J. C. CICCARELLI, L. J. BECKMAN, *Navigating Rough Waters. An Overview of Psychological Aspects of Surrogacy*, "Journal of Social Issues", 2005, 61(1), pp. 21-43.

[208] K. VORA, Indian Transnational Surrogacy and the Disaggregation of Mothering Work, "Anthropology News", 2009, 50(2), pp. 9-12; K. VORA, Indian Transnational Surrogacy and the Commodification of Vital Energy, "Subjectivity", 2009, 28(1), pp. 266- 278; K. VORA, Medicine, Markets and the Pregnant Body. Indian Commercial Surrogacy and Reproductive Labor in a Transnational Frame, "Scholar and Feminist Online – Critical Conceptions: Technology, Justice, and the Global Reproductive Market", 9(1/2), http://sfonline.barnard.edu/reprotech /vora_01.htm, 2011.

[209] A. PANDE, *Not an "Angel" Not a "Whore". Surrogates as "Dirty" Workers in India*, "Indian Journal of Gender Studies", 2009, 16(2), pp. 141-173.

home, maids, cleaners. it is however widely documented that these women make a conscious choice in undertaking gestation for others. If we consider that their previous work exposed them to many risks and hardships, and relegated them to the home and that in return they received scant and often uncertain wages, it comes as no surprise that their choice is consciously based on financial calculation[210]. Can we blame them? Cooper and Waldby explain that by working in the reproduction market women finally take on "an entrepreneurial economic role, even if in this way it exposes them to high risks for their body"[211].

Examining with a minimum of concreteness and seriousness the problems of carrying out gestation for others requires taking into account, on the one hand, the labour market and its relationship with international regulations and, on the other, the developments of scientific progress (without forgetting the way in which the common sense of morals modifies and how subjective desires change). This kind of approach takes time and method, but, although perhaps it is less accepted than the classic moral approach, it is the only way to shed light on a well-known but very unspoken truth: the labour market has always privileged the characteristics of women related to care and reproduction and this is why women have always been prisoners of stupid and humiliating myths. Rather than emanating bans, what is required is the affirmation of a different culture that values women for what they really are and which treats motherhood for what it really is, a feeling and not an instinct; and wanting to have a child only means that the feeling is present but not that that woman deserves more respect and should enjoy greater prestige, just as wanting to show compassion for a companion who cannot have children is a self-giving act that cannot be the object of derision and criticism. As for the modification of the common sense of morals, I will limit myself to recalling that the same Court of Human Rights has referred to it as the source of moral rule in a sort of appeal addressed to legislators, in its judgment prohibiting the donation of female gametes in force until a few years ago in Austria. It has been taken into account even by the Treccani Encyclopedia, the always careful guardian of our culture, that

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[210] According to reports by Cooper and Waldby women who choose surrogacy as a form of work receive compensation up to seven times their average annual income (about $ 7,000).

[211] M. COOPER, C. WALDBY, *Biolavoro Globale. Corpi e nuove forme di manodopera*, Derive-Approdi, Roma 2015, p. 117.

writes in this regard; "Ultimately, the new issues raised by IVF may require for many of us a change in the opinions inherited from traditional ethics." It must be recognized that such a profound transformation as the one foreseen concerning the reproductive function of family may involve a new ethics, with parameters different from those handed down by tradition. If it is true that the Biomedical Revolution, as a continuation of the Industrial Revolution, involves "the most fundamental transformation of humanity for which there are written documents", then it is reasonable to think that science is opening a new phase of history and that ancient paradigms must be questioned.

Statement in support of voting against the motion "Paid surrogacy" by Cinzia Caporale, Demetrio Neri and Grazia Zuffa.

Surrogacy as a practice has been used well before the spread of assisted reproductive technologies, despite the fact that they have encouraged its spread. The issue is controversial, as is evidenced by the different ethical sensitivity of female reflection, as well as the regulatory differences within Europe itself. It is also true that globalization increases the risks of exploitation and alienation, and of course we must ensure that women and their freedom are provided with adequate protection. Prohibition does not allow for such protection, it exposes women to the risks and abuse of the black market trade. Conversely, the choices of women during pregnancy and after childbirth should be guaranteed. Even by placing limits on agreements and contracts.

All this deserved a thorough investigational survey by the ICB as to today's reality regarding this practice and reflection on its meaning, starting from the experiences of the actual women who decide to carry out a pregnancy for another woman or couple. The stance adopted by the ICB, instead of probing and attentively listening, was to prefer to issue irrevocable judgment, closing the discussion before even starting it. Establishing that "surrogacy is a contract that damages the dignity of the woman and the child," means denying the existence of a human fabric surrounding the birth of those children, of investment, thoughts, desires, feelings, first and foremost on the part of the gestational mother. That is, the denial of women's subjectivity, considering them once again as "dumb" bodies, subject to requirements, to give birth or not to give birth, according to the will of others and not their own.

Presidenza del Consiglio dei Ministri



INFORMATION AND COMMUNICATION TECHNOLOGIES AND *BIG DATA*: BIOETHICAL ISSUES

25 November 2016

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Introduction

The advancement of information and communication technologies and the development of informatics are paving the way to new possibilities of knowledge, use and application in different fields, including healthcare. The expression big data refers to a massive volume of digital data constituted by the traces of personal information released into the environment through the use of information technology; this huge amount of data, coming from heterogeneous sources, is generated at great speed with pervasiveness.

The document discusses the enormous opportunities for development now opening up, especially in healthcare, with telemedicine, precision medicine, and the development of healthcare policies. The Committee also outlines some critical issues regarding the difficulty in governing the huge amount of data in the collection, analysis and use of data, particularly when it is used and applied differently from initial collection or without user awareness. Information technologies can present challenges regarding primarily processing and protection of private life and personal data, transparency, quality of information, addiction, the principle of participatory justice and governance.

The CNB, in view of an "appropriate" use of data, respectful of fundamental human rights, makes some recommendations: defining the responsibility of providers; verifying data quality and transparency of algorithms; identifying efficient instruments to request user consent or dissent to the processing of data; implementing an effective recognition of the right to be forgotten; involving citizens in emerging ethical issues, with special attention to young people, calling for the development of guidelines for the proper use of social technologies; promoting research for innovation of the ethical approach to the design of social technologies; guaranteeing all those who are willing to make use of new technologies conditions for access.

The Opinion calls for the development of legislation for the protection of personal data and the safeguarding of citizens/users against the social risks of misuse of data.

The annex includes a legal note retracing synthetically and in a critical manner the current situation of European and national regulation.

The subject and original draft of the Opinion was brought to the attention of the Committee by Prof. Rosaria Conte in April 2015.

Prof. Rosaria Conte presented in an internal consultation session the state of scientific and ethical discussion.

The group met twice in 2015. The preparation of the Opinion was interrupted because of Rosaria's ill health and death in the summer of 2016, which has left a great void.

Profs. Antonio Da Re, Lorenzo d'Avack, Laura Palazzani and Carlo Petrini have supplemented and completed the Opinion.

The Opinion was approved unanimously by those present on November 25, 2016, Profs. Salvatore Amato, Luisella Battaglia, Stefano Canestrari, Antonio Da Re, Lorenzo d'Avack, Riccardo Di Segni, Silvio Garattini, Marianna Gensabella, Assunta Morresi, Laura Palazzani, Monica Toraldo di Francia, Grazia Zuffa.

Dr. Maurizio Benato, Dr. Carlo Petrini, ex officio members , have also expressed their approval.

The Opinion was subsequently endorsed by Profs. Carlo Caltagirone, Cinzia Caporale, Carlo Casonato, Bruno Dallapiccola, Mario De Curtis, Carlo Flamigni, Paola Frati, Andrea Nicolussi, Rodolfo Proietti, Lucetta Scaraffia and ex officio members, Prof. Maria Teresa Palamara and Dr. Carla Bernasconi.

1. Preamble

In this document, the National Committee for Bioethics (CNB) refers to Information and Communication Technologies (ICT: Information and Communication Technologies) or the set of methods and technologies for the digital transmission and processing of information that enables or improves interaction between and with users at different levels (individuals, groups, communities, companies, organizations, institutions, etc.), with specific reference to the phenomenon of big data in relation to people's health.

The advancement of information technology (with the increase and acceleration in the collection, storage and processing of information) and the development of "data science" (i.e. the use of computing and mathematics with statistical techniques and algorithms) are opening up new possibilities of knowledge, use and application in various fields, including healthcare.

Particular reference will be made to: a) Social Technologies, i.e. the technologies employed by users to share content and technologies that provide information on possible partners for exchanges and cooperation (social networks); b) providers; c) search engines; d) user profiling techniques, which obtain/ derive/mine (relying on the use of complex algorithms) information from users, for diversified applications, including commercial applications, within the context of the so-called "digital revolution"[212].

In this context, the expression big data refers to massive digital data constituted by the traces of personal information released into the environment through the use of information technology[213], which is characterized by certain properties:

heterogeneity: different types of digital data and diverse supply sources (computers, mobile phones, the Internet, mobile devices and sensors, etc.); to traditional medical data (the results of laboratory testing, clinical records, epidemiological investigations) medical data coming from new technologies are added (genomic tests, results of body imaging or internet of the body,

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[212] S. SPIEKERMANN, A. ACQUISTI, R. BOEHME, K-L. HUI, *The Challenges of Personal Data Markets and Privacy*, in "Electronic Markets", 2015, 25, pp. 161-167.

[213] Not subject to analysis is the issue of *big data* from information derived from the use of genetic tests, genome-wide tests, which is analyzed in the Opinion *Managing "Incidental Findings" in genomic investigations with new technology platforms*, 17 March 2016.

electronic records, remote monitoring technologies or telemedicine);

numerosity: quantitative increase of data, it is becoming increasingly difficult to keep up with the updating of the unit of measurement (terabytes, petabytes, exabytes, etc.);

speed: exponential increase of connections and the data generation rate (it is very likely that in 2016 the number of connections on social networks will reach almost 19 billion);

ubiquity: unlimited expansion potential of data within the global network, and pervasiveness or invasiveness of possible data collection in all spheres of people's lives;

possible untruthfulness: the scarcity and possible lack of verification work on authenticity, accuracy and quality of information.

Users are induced and encouraged to provide information in exchange for other information; since any user action in the system turns into signaling, giving access to user features, users release a large amount of information to the benefit of the operators of these systems. ICT systems are therefore generators of collectively produced public and private information.

However, we will not be dealing with:

= educational platforms (such as MOOC, Massive Open Online Courses, or those supplied to specific telematic institutions) or entertainment systems (Secondlife, World of Warcraft, etc.), as they are not based on the collective provision of information[214];
= big data in developing countries with emerging economies, given that many problems have different connotations;
= security systems and systems of exchange and sharing (such as electronic markets and sharing economy systems), which despite being based on information provided by the user, and raising ethical concerns in a broad sense these do not present specific bioethical problems, which fall within the focus of attention of the Committee;

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[214] Moreover, in these systems, the high number of users is not as explosive as for other types of ICT (in 2015, 1 million on *secondlife*, 5 million on *world of warcraft* compared to 1 and a half billion on FB). Finally, the actual functionality of these systems is controversial: *secondlife* is for example considered by some a failure (it.finance.yahoo.com/notizie/che-fine-fatto-secondlife-07524429.html), even if the number of users of this system is not growing, neither is it reducing (www.downloadblog.it/post/21761/secondlife-dimenticato-dalla-stampa-ma-rimasto-solido-ed-amato).

= systems that use big data to detect collective political sensitivity and orientations, in order to achieve consensus and steer electoral choices.

The CNB has already partially dealt with some of these issues in previous Opinions: Ethics, health and new information technologies, 2006. The identification of the human body: bioethical aspects of biometrics, 2010 and Mobile Health Apps: bioethical aspects, in 2015.

2. Prospects for development and emerging ethical issues

Information technologies offer significant opportunities for economic and social development, and significantly enhance the individual's ability to acquire information and connect with other individuals as well as social and institutional entities, etc..

The expansion of ICT enables and will enable worldwide communication in the so-called "digital" society and allows digital citizens to obtain broad information in a simple manner, in their own language and in indefinite quantities. Major ICT systems in the future will lead us into an age of choices and unprecedented possibilities with a larger number of available data. The "explosion" of data and the "data revolution" will have spillovers on the world of politics, economy, and education.

At the same time, easy access and use of ICT permits almost everyone to use them. The only existing limits come from accessibility to the necessary technology (mobile phone, electricity) and a certain level of education so as to enable use (so-called "digital literacy"). The increasingly pervasive use of new information and communication technology in everyday life (everything we do leaves an informatic trace), makes us consciously or unconsciously, "users/contributors" of big data and our "digital" addiction, both personal and collective, tends to increase. On the other hand, it is not a question of stopping everything or moving backwards; not only is this impossible, but it would mean curbing a development process with enormous potential and promise.

Particularly significant paths of development in the field of health are taking shape with so-called "Data-driven precision medicine", (still the subject of study and research and currently not extended to all aspects of biology and medicine) this is the possibility to make, based on the amount of data

collected, predictions and simulations of diagnosis and treatments for individual patients in specific contexts or for stratified groups of patients (so-called personalized/stratified medicine or precision medicine), but it could possibly be extended to the definition of healthcare policies for public health and to prevention in particular. Moreover, ICT can improve and increase the efficiency of health services. As a matter of fact, there is a growing interpenetration between health care, information technologies and decisions taken regarding treatment. Cybermedicine is the all-encompassing term denominating this phenomenon, it is used to indicate the networking of a wide community of interests between various increasingly interdependent subjects who need this communicative exchange (national and local institutions, public health agencies with their own territorial organizations, private health organizations, health professionals, pharmacies and all the pharmaceutical sector, service companies and the suppliers of non-profit companies, voluntary and citizen associations).

Although we live in a deeply interconnected world, its modes of interconnectedness are only very broadly known to us: not only are we not in a position to know enough about the procedures and the paths that form our data as individuals, we are also not fully informed about how the data will actually be used, stored and for how long, who will use it and for what purpose, via which paths, who is responsible and to what extent. It is the existence of big data as such that makes it impossible to be truly and fully aware of this new universe.

However, a number of ethically problematic issues arise in relation to big data with specific reference to collection, analysis and use of data, particularly when it is used and applied differently from the initial collection or without the user's knowledge[215]. Information technologies can involve risks mainly related to the processing and protection of privacy and personal data, transparency, quality of information, addiction to ICT, even of a pathological kind, the principle of participatory justice and governance. The dangers relate mainly to: the misuse of data which causes harm to individuals, undue surveillance, stigmatization or discrimination. The scenarios may,

[215] For emerging ethical issues in ICT, see: European Group on Ethics in Science and New Technologies (EGE), *Ethics of Information and Communication Technologies*, 2012; reference to big data on *The Ethical implications of new health technologies and citizen participation*, 2015.

therefore, be complex and in some respects disquieting and yet insufficiently explored, especially regarding the impact on the health of citizens/clients.

2.1 Processing of personal data: challenges to privacy and informed consent

Contact with the virtual world starts from birth and entire stages of life are fixed in time and potentially made digitally visible to everyone. The exposure of "personal data" and "personal life" on the network raises the issue of privacy, minors especially are often unaware of this. The problem becomes even more complicated to tackle in a society which welcomes, values and promotes data "sharing" (information, images, videos).

The need for protection of the confidentiality of certain information and the means to defend one's virtual privacy should be highlighted from the earliest years of life, especially with the help of parents and educational systems. An education to active citizenship, which strives toward adaptation to our time (a kind of "Civic Education") cannot, by any means, underestimate the importance of these issues. Consequently, the recommendation to set up educational programs to enable users to develop this awareness within the context of acquiring a technical culture on instructions for internet use, is especially significant. This is particularly true as citizens risk losing much of the control they have on their private information in this virtual space through the expansion of data. The challenge presented to digital users lies in their gaining critical awareness of the problem, determining which devices and instruments they are able and willing to use, in order to avoid, as far as possible, losing control over their privacy.

One of the first ethical issues raised in the ethical and legal debate regarding ICT was the need for people to have sufficient control of their data when using the Internet, especially so-called sensitive data , including health data. The first regulations in the sector have specified the conditions applicable to the processing of data at the time of the request for information, which, should always be accompanied by explicit informed consent. This implies that there is transparency, completeness and simplicity in the information given by those who use and process information: they should specify who is collecting the data and who will use it, which data, how the data is collected, where it will be stored, for how long and for what reason and purpose. Consent must always be revocable, without producing negative

consequences for the user; and, unless the expression of consent provides otherwise, the right to access, rectify and delete personal data (so-called right to be forgotten) must remain[216] so that it is no longer accessible to the public in any form (copy or reproduction). Consent must always be able to provide an alternative computationally, i.e. refusal of consent (to provide information), setting out the implications. This means, in other words, transferring the concept of "traditional" informed consent from biomedicine to information technology.

In the age of big data we are witnessing a radical digital transformation which demands a change to both ethical and juridical approaches, with the re-signification of traditional categories; "privacy" being distinctly one of these. Many speak of "the end of" privacy, or of a concept destined to "evaporate". Even informed consent in its digital form is much more complex and requires structural rethinking. It is a matter of working out the new scenarios in which we find ourselves in the age of big data.

1) What information is collected?

The information requested of digital users is of an absolutely heterogeneous nature: for example, the information related to socio-demographic data (gender, age, marital status, education, affiliation, etc.) differ significantly from those relating to religion, political and ideological affiliation, and these in turn differ from the information concerning emotional states, attitudes, aptitudes, preferences and so on. What kind of information, therefore, is referred to when one authorizes the processing of personal data in the digital environment? The very concept of privacy is changing; it no longer just refers to the protection of "personal data," information relating

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[216] As argued in the ICB Opinion *The identification of the human body: bioethical profiles of biometrics,* 26 November 2010, "it must become an aspect of the fundamental right to personal identity, the right not to be catalogued, classified, possibly irreversibly marginalized on the basis of information obtained without one's knowledge, through non-transparent criteria and for largely unknown objectives. The growth, in terms of efficiency and security, biometric acquisitions should therefore be accompanied by a proportional increase of the possibilities of protection and hopefully of public awareness. If one cannot claim anonymity, it is essential that at least the conditions to be forgotten are guaranteed". The document by The European Group on Ethics in Science and New Technologies (EGE), *Ethics of Information and Communication Technologies,op. cit.,* suggests replacing the prevailing expression "*right to be forgotten*" with the "*right to data deletion*".

to an identified or identifiable, also indirectly, natural person by reference to any other information including a personal identification number and demographic information, but it extends to consideration of "personal life" or "private life" (which also includes information on biological data, behaviour, thoughts, feelings, personal communications, movements, groups etc.). Today, privacy means without any interference in private life, it is an appeal to discretion and confidentiality.

With specific regard to the data concerning health, consideration should also be given to the fact that boundaries between the strictly medical and non-medical spheres are becoming increasingly blurred, like those between health and society; information on lifestyles and behaviours tends to become increasingly more relevant to health even within the perspective of prevention. In this sense, health information is considered to be not only the results of laboratory tests or epidemiological data, but also the general news that comes from social networks.

2) How is information collected?

Whatever the type of information, it is difficult to ensure the individuals' full awareness at the time of consenting to the processing of their data: in the everyday practical use of network services, users are inattentive and in a hurry, they do not stop to carefully read the contracts they sign (frequently displayed on a screen, written in small type, in multiple pages) in order to access the service that is of interest to them. In addition to this; users - and this is particularly true in the case of network information managers - do not know how this information was obtained, nor what specific uses it allows, they do not know or do not remember if and what they previously consented to. For instance, the case of the information that can be obtained by clicking on like once users are signed up on social network pages. Even if those registered know that their like can be a valuable source of information for that particular service provider, they do not know how these likes are treated. At the same time users can not be said to be completely free when faced with the alternative of either handing over their data or being compelled to terminate use of the social network service. Or indeed, when free services (e.g. access to music etc.) are offered in exchange for the "bestowal" of data.

3) Who collects and stores the data? For what purpose? Where are they stored?

In regards to the quantity of data collected and processing modalities, the individual user is hardly able to understand the potentialities held by those collecting this data. It is generally not explained to the user who collects the data (the phone company if collected by cell phone? the provider if collected by computer?). "Network information managers" (both public and private) collect data in aggregate form, with the ability to mine information (this is the basis of the economic attractiveness of data). It must also be taken into account that, currently, online platforms (in particular private managers) can forward or sell the data as "macro-aggregates" to other companies (if not legally prohibited) without asking for specific and precise consent, with the result that people communicate information about their lives to a much greater extent than they are actually aware of.

There is "in principle" a difference between the potential uses of data and the associated risks: their use differs for commercial purposes (e.g. the use of data to identify categories for advertising and marketing purposes) or scientific use (e.g. the sharing of health information within services/pathways of care, for the purpose of clinical-epidemiological research). It is not easy to make this distinction; in most cases the boundary between scientific research and market research becomes blurred and indistinguishable, at the expense of the unwitting digital user (e.g. think of the "PatientsLikeMe" platform, where scientific research and commercial research are closely and indistinctly connected).

Moreover, even assuming the possibility that all information is clearly expressed and communicated to users (regarding the collection, storage and use of data), there is the problem of its actual intelligibility, given the quantity of information and the complexity of content (just think of what it means to explain and understand the meaning and functionality of an "algorithm" or to explain the concept of a person's private life and dignity), and given the lack of interaction with the user to allow for assessment of suitability (as opposed to informed consent which is obtained after information is given by the doctor to the patient).

This results, inevitably, in a "challenge" to informed consent as it has been traditionally understood, which by contrast requires reformulation fol-

lowing new paths, possibly providing for differentiated modalities of informed consent according to the context.

Informed consent, in the field of big data, cannot be specific (as in the case, for example, of "traditional" medical consent); it, inevitably, calls for characteristics of "broadness" given the impossibility of accurately anticipating the paths of research (similar to what occurs within the framework of biobanks); it is therefore a "dynamic" and "flexible" consent, which identifies similar areas of research directly or indirectly related to the original path. Broadness, dynamism and flexibility do not mean "blind" consent to whatever research.

One could perhaps rethink the very expression "Informed consent" in the digital world, limiting it to an "awareness" or "acknowledgement" that the data will be collected, in the critical consciousness of the impossibility of anonymity (re-identification is always possible, i.e. by crossing information user identity is traced back), in the non-precise a priori determination of the method of use, storage, and analysis of data, and the impossibility to guarantee security and confidentiality in all circumstances.

It should also be considered that the need to introduce, in a precise manner, the use of consent for each specific step in the use and application of data could provoke exactly the opposite reaction in the digital user; instead of increasing the user's attention to problems, it could increase haste and divert attention away from the actual subject matter of the consent. Consider the use of consent to cookies: one can not fail to point out that faced with the legitimate concern over the use of the information obtained by "clicking" on various web pages, the request mechanism has become so pervasive that the user generally does not read the disclosures and ends up giving consent indiscriminately whenever so requested. Web browsing would, otherwise, be dedicated most of the time to reading disclosure documents on privacy.

Given these uncertain scenarios, and in particular the blurred boundaries between scientific research and commercial research, it is possible to envisage that individuals may a priori express themselves at least under certain "minimum conditions", with a request for a posteriori verification: by requiring that data be provided only on condition that both the subject acquiring it (distinguishing at least between public and private institutions) and the purpose of the data transfer are known; demanding transparency

and interactive participation (with online portals that facilitate communication), dynamic communication of research findings, the possibility to "opt-out" or exit the research if it takes paths that the user does not agree with and, consequently, delete the data from that moment; defining the areas of research to which the user objects (for example, objection to the use of information for research in the military sphere or other sphere).

We must remember that the individuals themselves are willing to "share" information, not keep data private and actively participate in research. The important thing is their being aware of the possible implications of this active participation and sharing and the actual possibility of opting out of any research.

An emerging specific problem in healthcare is the relationship between mandatory transfer/sharing of data and insurance. The customers/digital users should be free to send or not send information about their habits, lifestyles, preferences; insurance tend to encourage the sharing of data, and to adjust costs/premiums on the basis of sharing and lifestyle habits. Therefore the customer/insurance relationship is shifting from the recording of medical data to even sharing lifestyle habits, which can lead the unsuspecting user into hidden forms of control which limit individual freedom on the basis of a predefined "standardisation" of behaviour considered to be "best" (but who should define the standards?; should this not be assessed on a case by case basis?). The same problem arises in the context of the employment between workers or potential workers and employers.

2.2 Transparency: the ethics of algorithms and network neutrality

One of the most ethically problematic elements of big data, particularly in the context of health applications, consists in the use of algorithms. Massive data collection is generally random and based on the statistical frequency of behaviour, but the selection in the use of data/information, the creation of (non- causal) relationships between information and predictions (i.e. the configuration of likely future scenarios, behaviour, etc.) are built from algorithms, developed by mathematicians and computer scientists. Algorithms calculate on the basis of variables, seeking correlations, outlining predictions.

It is important to introduce some considerations. Selected behaviour is only frequent behaviour; frequency is the key element of a statistical sur-

vey. With the result that infrequent (isolated or rare) behaviour risks being marginalized in the digital age, with the possibility that people tend, in order to be recognizable in the digital world, to conform to the most common or repeated behaviour in society. The pressure of homologation, conformity of behaviour (as well as the pressure to share) highlights the reduction of the space for freedom in the era of big data. Instead, we should make the digital user conscious of the fact that algorithms construct correlations and predictions regarding (mathematically calculated) "probability" that does not coincide with reality (or evidence, causality, unpredictability, which must remain possible and imaginable). Algorithms construct an identity that becomes ever more collective. We speak of group identity. It is profiling, which identifies the major and minor probability or propensity to act in certain ways, of certain stratified groups of individuals.

What criteria form the basis on which algorithms are constructed? The ethical importance of transparency in the use of the algorithms used by providers relate to the release and processing of personal data.

An important aspect therefore concerns the full publication of all the factors which research algorithms take into account. Is it acceptable that the trade secret should be extended to cover even the factors that come into play in the algorithm used by the search engine? This question is of ethical importance for at least two reasons. In the first place, only a part of the factors in question are currently in the public domain, encouraging in users the illusory belief that these are, or predominantly are, the factors used. Secondly, network information providers play an increasingly decisive role in the formation of so-called public opinion. However, the opacity of the factors upon which search engines are based does not allow the monitoring of the quality of information and possible manipulation of public opinion itself via the network.

The lack of transparency therefore takes on greater significance on the ethical level when we consider the role of advertising in ordering the results of a network search. Nothing prevents from associating the advertisements that pay more to the most comprehensive websites in terms of information. The opposite - that is, ordering websites by taking into account advertisements that provide the greatest income to the provider - is ethically untenable.

It is one of the most complex questions, connected with transparency: Who has the power to decide what information is appropriate to be shared

and what should be amended, even temporarily? There are opposing views on the matter. Some believe that a certain level of supervision is necessary for any computer platform, if you want it to play a positive role in society. Others believe that it is tangibly impracticable and cite the illegal activities of hackers. But they also add that if there is a central organization or interest or pressure groups that establish or promote the release of information, then there is the risk of non-transparent information, controlled by the ideas and ideologies of those taking such decisions and this is true no matter how transparent or neutral the actual platforms may be. These concerns, growing in non-democratic political regimes, lead to the belief that data maintained over time constitute a "control" system by society to the powers that be, even in the face of negative consequences (security threats, scarce protection of privacy, the interests of organizations, etc.). The more extensive the documentation is, the greater the possibility of obtaining exhaustive information, making conscious choices, informing future generations.

The latter thesis has not to date been accepted among governments and Western societies, concerned about the risks involved with deficient information security. It follows that, it is possible to note the investment of resources increasingly aimed at improving the protection of data and documents.

2.3 Truthfulness and quality of information: possible bioethical implications

Some IT phenomena show the problematic nature of truthfulness and the quality of information, highlighting the "opacity" of certain technologies. Examples are the information bubble and the hidden factors within the framework of search engines, which can have negative health implications.

Search engines are services that enable the identification of websites of interest to the user, in exchange for profiling the actual user[217]. These

[217] There is a search engine that does not track our data, that is, which does not commercially exploit our input, differently from what , for example, Google does. It is a search engine (duckduckgo.com) already available online and immediately available to the citizen browser; for more information on this, see the article published in www.fastweb.it/web-e-digital/duckduckgo-il-motore-di-ricerca-che-tutela-la-privacy, dedicated to the operational aspect of the search engine and its history. Duckduckgo.com is an interesting and concrete reality on which to reflect, a reality that is growing, which is not a niche (something like 10 million daily searches). It could be a temporary remedy offered to citizens for better protection of their privacy and their browsing, an easy remedy to apply, with an immediate impact.

search algorithms are the subject of debate within the scientific community and beyond. In particular, their properties generate at least two[218] fundamental problems:

Information bubble

Through the search algorithm used by providers and the properties of social networks, users are progressively separated from information that contrasts with their point of view and are intellectually isolated in their "information bubble". Someone searching on the internet for "BP" obtains information on the investments of British Petroleum, while someone else may obtain information on the disaster of the Deepwater Horizon of 2010 also known as BP disaster. The web pages can also be very different from each other. The information bubble works as a "personal" ecosystem or as an "ideological"[219] frame. It is potentially harmful for the individual and for society, restricting the spread of counter-arguments, rebuttals, evidence of opinions and accepted hypotheses. Since one of the algorithm filters is the personal characteristics of users, they end up being trapped in an information bubble. One could speculate that the "weakest" individuals are more prone to this effect because their searches on search engines can be used/exploited for commercial purposes, that is, for advertising goods to them to compensate or solve their "difficulties". These may be "difficulties" of every kind: affective and relational deficiencies, diseases, economic poverty, etc. In this case, the "weak" are those who (i) have such difficulties and who (ii) have less information or fewer computer skills or less computer malice, i.e. teenagers, the elderly, adult users who have started using the internet and social networks, without prior training.

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[218] Instead a third effect is not univocally confirmed known as googlearcy or googlocracy. According to some scholars, the *PageRank* would produce a *power-law* distribution of information: the pages with high rank would be more likely to be visited, creating a vicious circle, i.e. boosting the popularity of the most popular sites. The topic is controversial in reality. According to other scholars, the use of search engines could even have an egalitarian effect, when compared with a random search algorithm on the web or with the research done by users starting with known sites.

[219] *In The Filter Bubble* (E. PARISER, *Il filtro. Quello che internet nasconde*, Il Saggiatore, Milan 2012) we observe how, through filters, "the creators of customization offer us a made to measure world, every aspect of which corresponds perfectly to our tastes. It is a reassuring way, populated by our people, things and favourite ideas" (E. PARISER, Il filtro, p. 16). According to the author, filter bubbles harm society because they make people more vulnerable and exposed to propaganda and manipulation.

Hidden factors

According to some sources, the pages at the top of the ranking are those which associate advertising from which the company receives the most money[220]. These affirmations have not been denied.

PageRank is transparent, but there is a list of criteria that IT companies will take into account[221] that also contains hundreds of factors. This list is not official. Some specialists in the field of search engines have developed a hypothetical list based on their own experience and on empirical data[222]. Officially, IT companies merely declare to take into consideration factors in the ordering of pages, but they do not publish the algorithm, as it is a trade secret. The user therefore does not know how these data are used and aggregated. We only know that PageRank is one of these factors.

What are the bioethical implications of these critical issues? Think of a sick person searching for cures through these search engines. This allows the search engine to gather this input and customize the future online browsing of the sick person (i.e. the dynamics of the information bubble), forcing him (i) to think and mull over the illness every time he browses the internet; (ii) display advertisements of unsubstantiated treatments; (iii) lead to the increased belief in the reliability of these adverts ("I saw it on the Internet!" , "Dr. .... who also has a personal website with testimonials from the cured smiling patients!", "If this announcement is so recurrent, it must be reliable") with the possibility of renouncing to the care channels close to him that are, above all, consolidated (e.g. general practitioner, pharmacist, emergency department, etc.). This mechanism can also be found in other particularly " weak" figures, as previously outlined. In summary, the "weakest" can get into a vicious circle fuelled by their "difficulties", but accelerated by indexation for commercial purpose (big data) that search engines and so-

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[220] See for general explanations and detail, respectively: support.google.com/adwords/answer/2497976?hl=en&ref_topic=3121763 and support.google.com/adwords/answer/1752122.

[221] See the list by following the link www.searchenginejournal.com/infographic-googles-200-ranking-factors/64316/).

[222] An example of a study performed to identify the factors and the relative importance is reported in https://moz.com/search-ranking-factors. Every two years or so, Moz carries out an investigation to identify the most important factors influencing research in moz.com/search-ranking-factors network. A more precise study on the time scale is reported in www.cnet.com/news/testing-googles-panda-algorithm-cnet-analysis.

cial networking use. The information bubble becomes a kind of (well hidden) trap for those who are "weakest".

Consider then that 72% of people who use the Internet, use this tool for biomedical information[223], but unfortunately the number, variety, and impact of biomedical "scams" is rather staggering[224]. It is not just about therapeutic scams - which represent a large subset of misinformation in the biomedical field - but also myths and conspiracy theories, pharmaceutical "discoveries" that have been proven to be outright frauds; fallacies in diagnostic reasoning and identification of apparent diseases; false information concerning the correlation between existing diseases or on prevention methods - foremost among all being vaccines; crusades against official therapies (in the case of chemotherapy, against which often healers and charlatans are active).

The easy money made from bogus therapies and useless, if not dangerous, practices, are not apparently the only reason for the prompt and broad dissemination of misinformation in the medical field (which apparently has an ancient history[225]). Some properties of large communication technologies facilitate the dissemination of scams. The quality of the information in circulation, upon which public health is dependent, depends largely on the properties of the technological instruments at our disposal. One, alarming proof: the impact of the anti-vaccine movement measured by the cumulative number of new cases of measles per month in the USA, for each year from 2001 to 2014. According to CDC data, last year alone, there were 644 new cases of measles in the 27 states of the Union. This is the largest number of cases ever seen for over a quarter century[226]. Vigilance is

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[223] *Cfr.* slideplayer.it/slide/3649692.

[224] In medbunker.blogspot.it; *cfr.* Even www.healthonnet.org/HONcode/Italian/?HONConduct117222.

[225] S.CASILLO, F.DI TROCCHIO, S. SICA, *Falsi giornalistici. Finti scoop e bufale quotidiane*, Guida, Milan 1997.

[226] Data from www.gravita-zero.org/2015/01/vaccini-negazionisti-movimento-antivaccini.html.

[227] In confirmation of the above, on 09.10.2016 we carried out a review of the results that emerge from the Google search engine by typing the combination "vaccine/autism." The resulting data are certainly interesting (and worrying). Considering that the first ten sites resulting from the combined research of both terms, one can argue that five dismiss any justification for the alleged correlation between vaccination and the onset of autism; three instead are openly opposed to vaccination, they use a highly polemical and alarmist tone, and allude to the existence of possible conspiracies, as such obviously not verifiable;

needed on information tools to protect the quality of information and, ultimately, public health[227].

2.4 Addiction: a further bioethical implication

A critical issue of evident bioethical importance is the fact that ICT can also create various forms of addiction. There is talk about Internet Addiction Disorder (IAD). In the scientific community there is substantial convergence in the recognition that internet addiction has negative repercussions on an individual's life; above all, the relational dimension of life is affected, as it is strongly compressed and actually hinders the real conditions of everyday life, from work to family, to being generally more present in society. It is more problematic to establish whether these certainly negative effects represent a real disorder, comparable for example to drug addiction. In this regard, it should be noted that the latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) does not include Internet Addiction Disorder within the diagnostic category of behavioural addictions, suggesting therefore that at present there is insufficient evidence about it. Internet Gaming Disorder, has, however, been included with the specification that it is still necessary to develop additional research to determine whether it can be considered in all respects a pathological disorder.

The fact is that up to a certain point the negative effects of compulsive Internet use were assessed in relation to specific activities such as online pornography and gambling; subsequently it has been suggested that these effects also affect uncontrolled browsing in general, carried out in the most diverse contexts[228]. There are seven symptoms that may indicate some form

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two sites instead remain on a more descriptive level, reporting of some cases in the news. It may be reassuring that the majority presence in the top ten, well-documented sites recommend the use of vaccination, based on proven scientific research and the reference to significant epidemiological data; however it is disconcerting to discover that the three anti-vaccination sites are respectively placed in second, third and fourth place, therefore in the most immediate positions, ready to be clicked. Of course, these sites omit to recall that "the scientific publications that supported a causal link between vaccination and onset of autism have been reprocessed and (...) the lead author of this theories has been convicted of fraud" in Italian Committee for Bioethics, *The importance of vaccinations*, the motion of April 24, 2015).

[228] *Cfr.* K.W. MULLER *et al.*, *A Hidden Type of Internet Addiction? Intense and Addictive Use of Social Networking Sites in Adolescents*, "Computers in Human Behavior", 2016, 55, pp. 172-177; K. YUNG *et al.*, *Internet Addiction Disorder and Problematic Use of Google Glass ™ in Patient Treated at a Residential Substance Abuse Treatment Program*, "Addictive Behaviors", 2015, 41, pp. 58-60.

of disorder linked to the use of the internet: personal satisfaction derived from the time spent web browsing, little interest in other activities, anxiety and depression when without access to the network, urgent need to control events on the web, increasing frequency of use of the internet compared to usual habits, long connection times and network usage even in the event of concrete work and social impediments.

Five profiles have been detected according to the addiction: cyber-sexual addiction (related to pornography), net-compulsion (gambling and shopping), information overload (frantic search for information), cyber-relations addiction (social networking abuse) and computer addiction (excessive use of online games).

2.5 Participatory Justice

Another issue worthy of mention is that of the access to these technologies. There is, today, a "digital divide" because of age, socio-economic status, and geographical area: the elderly, the less educated, the inhabitants of developing countries are the most vulnerable in the digital age.

Given the positive elements of being connected to the internet, equal access should be guaranteed, allowing everyone to acquire the tools, knowledge, skills and motivation to use new information technologies in order to participate democratically within the global society and not be marginalized from the network. At the same time, there must be guarantees - at least temporarily, pending the implementation of technology – of an alternative access to services (especially in the health sector) to people or groups who have neither the technologies nor the skills to use them. The objective should be to enable everyone to participate according to the principle of equality, equal opportunities and non-discrimination.

What needs to be avoided is the so called "two-speed medical system": fast for those who have new technologies at their disposal and slow for those who can not join in. Together with equal access, there should also be equality in educating to access ICT in a conscious and critical manner in relation to emerging ethical issues. Furthermore, the positive results of ICT use for health should be shared by everyone, according to the increasingly consolidated principle in global bioethics of "benefit sharing".

There should, therefore, be implementation of the instruments which stimulate users to take part in digital initiatives that provide new opportu-

nities for comparison, sharing, and knowledge. Think of the new platforms created to allow the subjects participating in trials to be constantly updated on the progress of research; to platforms developed to allow sharing among patients, especially useful and valuable in the sphere of rare diseases.

2.6 Governance

ICTs and big data have therefore made problematic concepts like, privacy, self-determination, informed consent and, in the final analysis, also individual rights, as known and treated, until now. This is why the protection of security and privacy (understood, as mentioned, in a broader sense) should be a shared responsibility between users, companies, and institutions. There is debate about whether IT companies in addition to contending the hosting of genomic data[229], should put in place effective tools which can enable users to gain awareness; there is debate on the importance of institutions to plan effective governance in this area. It will be specifically up to the latter to exploit these possibilities properly in full awareness that, in the face of accumulation of data, non-use results in a loss of privacy and security. Moreover, it is known to computer scientists that the so-called "delete" key does not guarantee the loss of files, e-mails and messages, which can be recovered very easily (data persistence). This digital knowledge of any citizen, carrying out public or professional activities, can and may produce significant consequences within society. The documented past of citizens can be recovered and used to influence their image in the workplace and in everyday life.

The context so far briefly described is already, in itself, sufficient in order to grasp why the governance and regulation of data collection and related storage procedures are destined to significantly affect not only the protection of individuals and groups, but also the interests of those who are intent on economically exploiting such information. Certainly the facilities which organize large data centres, involved in concentrating the space of the information, will be protected, although the logic of centralization makes

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[229] J.T. WILBANKS, E. J. TOPOL, *Stop the Privatization of Health Data. Tech Giants Moving into May Widen Health Inequalities Research and Harm, Unless People Can Access and Share Their data*, "Nature", 2016, 535 (7612), pp. 21-27.

these data centres very attractive targets for the perpetrators of data theft. In fact, if the information is of commercial value for businesses, if it becomes a bargaining chip between them and partly between enterprises and customers, it is obvious that this information is also sought-after by those who are motivated by the desire to obtain an illegal profit, that is, in a different context, such as the political one, it is a tool that enables outright cyber war.

Therefore, there should be a strengthening of data protection mechanisms and defence of their systems from hackers. However, in the face of a common will, in all countries where the digital economy has gained ground, to regulate precisely this, illegitimate access to data, on the other hand there is a noticeable difficulty in defining the rules governing this matter. We are in a borderline area where, the security needs of individuals, the lobbying interests of sector enterprises, the will of States to guarantee an efficient and secure information ecosystem, all intersect. The balancing of these conflicting requirements, in the global international scene, is achieved with different perspectives in account of the different way to consider and relate the data once as merchandise then as parts of the personality, and also in consideration of the different forms of government, which have an impact on greater or lesser degree of control and protection of personal data (think of repressive models in different parts of the world). However, the sharing of the interests involved may well enable to initiate dialogue on these needs between the various regulatory models, in order to facilitate convergence towards shared solutions. Convergent solutions are increasingly necessary given the globalization of information and inevitable "trans-border" transfer of information.

However, greater attention to the virtual community is now spreading among technology companies; this attention is reflected in the tendency that all online products and services provide for the user's acceptance of terms and conditions in accordance with contractual guidelines. Even legislators increasingly feel the need to support the assertion of the centrality of consent by establishing specific authorities endowed with analytical and control abilities, which the individual user lacks, and which are capable of influencing the policies adopted by ICT enterprises. But the fact remains that, notwithstanding these efforts in favour of user guarantees, the citizen must be well aware that protecting a person whose data end up on the Web is very difficult, due to lack of effective tools and the fact that protection is mainly in

the user's own hands, at the moment of assessing the quality of the product, but also the ease with which companies enable monitoring and guarantee confidentiality.

The difficulty in regulating the matter should not lead the legislator to renounce his duties: drawing up norms to safeguard not only the protection of personal data (confidentiality, discretion, privacy)[230], but also personal freedom[231] with appropriate anti-discrimination laws, which permit to exercise proper supervision of the "social risks" of new technologies. There is a particular requirement for regulatory instruments to punish the misuse of personal data and information on the private life of users or the publicizing of unauthorized computer materials for denigrating purposes; punishing the intentional use of algorithms that on a purely predictive level (compared to habits and behaviours) produce as a result the marginalization of "minority" categories with social stigma.

3. Recommendations

In light of the above considerations, the CNB intends to underline that in the era of big data the problem consists not so much in the use of data, but in the "appropriate" use of data for the good of mankind and health. To this end, the CNB therefore makes the following recommendations:

to Identify and define the responsibility of providers, especially in certain circumstances, in which there are special social conditions of risk: this responsibility should not be restricted to the declaration related to the commercial use of personal data, but it should be extended to review the quality of data and the transparency of search engine algorithms; committing the authorities for information and communication to proper monitoring;

to identify efficient instruments to obtain consent or withhold consent

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[230] This is the approach promoted in the document F. CALDICOTT (ed.), *Information: to Share or not to Share? The Information Governance Review,* March 2013. It underlines the need, in the context of health, to balance the need for privacy with the need for information sharing between doctors and healthcare workers in the interest of the patient and public health.

[231] C. BOCK, *Preserve Personal Freedom in Networked Societies. Broad Anti-Discrimination Laws and Practices could Compensate for Failing Data Protection and Technology-Linked Loss of Privacy,* "Nature", 2016, 537 (7618), p. 9.

to the processing of user data, based on synthetic and easily readable information about the type of data and method of collection, the purposes for which they are used as well as the related procedures for processing and analysis. Should such information not be provided, the user must, in any case, explicitly demonstrate his/her awareness of the limits to privacy, the possibility of re-identification, the possible uses including commercial use of data;

to implement effective recognition of the right to be forgotten, establishing through clear and transparent procedures the possibility for the data subject to request deletion of personal data, so that these are no longer accessible to the public under any form (copy or reproduction);

to promote press campaigns, advertising campaigns (e.g. Public Information films), and educational programmes on the functioning of social technologies that handle information between users or between users and managers. The aim is to actively involve users and allow for critical awareness of the emerging ethical issues of new technologies, especially for particularly vulnerable persons, as well as making them aware of possible risks in the networking and sharing of information;

to urge public healthcare institutions at various levels, to prepare and to keep updated an information website, on which citizens may find confirmation or official denial of the accuracy and quality of medical news[232];

to urge the Ministry of Education to draw up and distribute in schools Guidelines for proper use of social technologies. We must foster the emergence of a new "netiquette"[233], which prescribes socially and psychologically sustainable use, ethical awareness of the risks of the Internet and social networks, with a special emphasis on health-related issues. One should from the earliest years of life, especially with the help of parents and school systems, highlight the need to protect the confidentiality of certain information and the means of defending one's own virtual privacy. An education to active citizenship, which aims to be appropriate to the times (a kind of civic education 2.0.) can in no way underestimate the importance of these issues.

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[232] The Italian National Institute of Health is certainly moving in this direction by setting up a so-called *Knowledge Portal*, which will be available shortly.

[233] The term refers to the *network* (net) and *etiquette* (good manners).

Consequently the recommendation for the setting up of educational programs that enable users to develop this awareness in the context of a technical culture on the use of the internet[234];

to support research for innovation in the ethical approach to the design of social technologies. So far, ethics in ICT has essentially been confined to the protection of privacy. But as we have seen, this is just one of the ethical problems that social technologies present. Investment is needed for research on bioethically compatible systems. For example, in order to curb the phenomenon of addiction, it is possible to imagine automated alerting systems to alert the user of having crossed a critical threshold in connection time. Even the automatic offer of self-assessment tools, to be administered prior to establishing the connection (a kind of health cookie) could make users more aware of the risks they run;

to guarantee conditions for access to all those who intend to make use of new technologies, and at the same time guarantee the rights of those who can not/do not want to connect, specifically as regards access to health services for citizens.

Urging discipline for the protection of personal data (based on the protection of privacy and confidentiality, minimization of the use of sensitive data, justification and proportionality of collection, the responsibility of those who use the data); urging also the adoption of regulations aimed at providing adequate anti-discrimination laws, which help to avoid or at least mitigate the social risks of misuse of virtual data: the aim is to protect, not only personal data, but above all the personal freedom of citizens.

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[234] It goes without saying that this kind of *Civic Education* 2.0 could also address topics and issues that have a direct bioethical relevance, consistent with what had been called for by the Memorandum of Understanding between the Ministry of Education and the ICB signed on 15/7/2010. This protocol identified in bioethical education, to be promoted within the school system, one possible exemplification of the more general training devoted to *Citizenship and Constitution*.

Annex: Legal note

In Italy the processing of personal data is protected first by law 675 of 31 December 1996 "Protection of persons and other subjects regarding the processing of personal data", later repealed under art.183, paragraph 1, letter a) subsequent legislative decree no. 196 of 30 June 2003 ("Code regarding the protection of personal data") currently in force. According to the Code the processing of personal data should be based on principles of fairness, legality and transparency and protection of privacy and the rights of those providing them.

Significant changes to the legislation were made by the legislature with D.L. 69/2012 on implementation of the 2009/136/EC directives on processing of personal data and protection of privacy in the electronic communications sector, and the EC Regulation n. No 2006/2004 on cooperation between national authorities responsible for the enforcement of consumer protection. A series of changes that are contextualized in the more general view of the dynamics inherent in the movement of personal data and their exploitation for commercial purposes, in the light of the emerging reform policies in this area both in Europe and in different parts of the world. Specifically, the two central themes at issue in the D.L. are the profiling of users while browsing online, and the management of data breach events and this is because of the growing importance of the predictive key assumed by information, and in particular by personal information, in the most advanced economies.

The Italian Data Protection Authority enacted measures: n. 229 of 8 May 2014 relating to the "identification of simplified procedures for information and the acquisition of consent for the use of cookies" and n. 353 of July 10, 2014 against Google Inc. on the "compliance with the Code of processing of personal data carried out under the new privacy policy"; March 19, 2015 the "Guidelines concerning the processing of personal data for profiling online"[235].

The Guarantor ruled that the network service provider (search engines,

[235] Published in the Official Gazette of May 6, 2015 (Guidelines). See the website: www.portolano.it/pcc_newsletters/profilazione-online-le-linee-guida-del-garante-privacy.

email, social networks, cloud, online payments, statistics and visitor tracking website analysis, etc.) shall not use data for profiling purposes, without the consent of the user, and that this activity for commercial purposes must be explicitly declared. This is the first measure of its kind in Europe, it emerged as part of a coordinated action with other European authorities and following the ruling of the European Court of Justice on the right to be forgotten. In summary, the Guidelines are intended to ensure that all providers of information society services, as well as all those who offer their users online services accessible to the public through electronic communications networks, with specific regard to the processing of personal data relating to the use of the features offered, taking into account in particular: - the information given to those concerned in art. 13 of the Code and as set out in paragraph 3 of these Guidelines; - the prior consent of users and information about them, even deriving from processing, in automated mode, of the personal details of users authenticated in relation to the use of the transmission and reception of e-mail messages service; - the respect of the right of objection provided for in Article. 7 of the Code; - the adoption of a data retention policy compliant with the purposes of art. 11 of the Code[236].

As part of the processing of sensitive data at the European level (although not specifically related to big data) we must remember Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of data, subsequently repealed by Commission Regulation (EU) 2016/679 of the European Parliament and of the Council on 27 April 2016[237] (which will be described below) and Directive 2002/58/EC of the Parliament European Parliament and Council on 12 July 2002 concerning the processing of personal data and the protection of privacy in the electronic communications sector, then amended by Directive 2009/136.

Among the most significant documents on the subject adopted by the

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[236] For an illustration of the Guidelines and the required measures see www.diritto24.ilsole24ore.com/art/guidaAlDiritto/dirittoCivile/2014-07-21/google-garante-trasparenza-profilazione-125008.php?refresh_ce= 1.

[237] European Parliament, EU Council. Regulation (EU) 2016/679 of the European Parliament and of the Council, on 27 April 2016 on the protection of individuals with regard to the processing of personal data and on the free movement of such data and repealing Directive 95/46 / EC (general Regulation on data protection). Official Journal of the European Union May 4, 2016, L119: pp. 1-88.

Council of Europe are: Convention for the protection of individuals with regard to automatic processing of personal data, Council of Europe, 1981 and additional protocol (Additional Protocol to Convention ETS No.108 on Supervisory Authorities and Transborder Data Flows); Recommendation CM/Rec (2010)13 of the Committee of Ministers to member states on the protection of individuals with regard to automatic processing of personal data in the context of profiling (23 November 2010); Recommendation CM/Rec (2010)13 on the protection of individuals with regard to automatic processing of personal data in the context of profiling (23 November 2010); Recommendation CM/Rec (2012)4 on the protection of human rights with regard to social networking services; Recommendation CM/Rec (2014)6 on human rights for Internet users; Recommendation CM/Rec (2016)1 on protecting and promoting the right to freedom of expression and the right to private life with regard to network neutrality.

It should also be noted that, the European Union Court of Justice[238] has recently invalidated a previous decision of the European Commission (2000/520/EC), which ascertained adequate protection for privacy even of personal data transferred to the United States (so-called Safe Harbour system). Obstructing de facto national authorities verifying the level of security guaranteed to data overseas and failing to provide any mechanism for updating the Safe Harbor criteria, the decision of the Commission in 2000 was deemed to be detrimental to the essential content of the right to respect for private life, allowing, for example, US public authorities access across the board to the content of electronic communications transferred there, even for profiling purposes. By doing so the Court of Justice has given back to individual national authorities the power to judge the appropriateness of the security levels of transferred data, inviting, at least implicitly, the Commission to renegotiate the agreement on the transfer of data. More recently on July 12, 2016 the European Commission adopted an agreement to safeguard "the fundamental rights of any person in the EU whose personal data are transferred to the United States" and bring about "legal clarity to companies operating transatlantic data transfers". In the EU-US shield for privacy, there

[238] Judgment of 6 October 2015, Case C-362/14, Maximillian Schrems / Data Protection Commissioner.

have been some specific provisions included on the subject of health data[239].

Finally, the processing of personal data has drawn the attention of the European Parliament and the Court of Justice also with regard to the protection of natural persons as to the processing of personal data in the course of investigations and detection of crimes and on the free movement of such data. In particular, both the (EU) Directive 2016/680[240] issued by the European Parliament and the Council on 27 April 2016, and the aforementioned (EU) Regulation 2016/679[241] issued on the same date, place at the basis of protection of the parties concerned, i.e. those referred to by the personal information, "the data subject should have the right not to be subject to a decision evaluating personal aspects relating to him or her which is based solely on automated processing and which (...) significantly affects, him or her. In any case, such processing should be subject to suitable safeguards, including the provision of specific information to the data subject (...)" (art. 38 Directive).

While Directive 2016/680 relates specifically to the processing of personal data by competent authorities for the prevention, investigation, detection and prosecution of criminal offenses or the execution of criminal sanctions, Regulation 2016/679 is of great importance for information and communication technologies because, among other things, it provides the basis for the exercise of new rights and defines limits with regard to the automatic processing of personal data.

The Regulation states that the persons involved in the processing of personal data should be informed of their right to revoke consent to certain processing, including, for example, processing for the purpose of direct marketing. It also stipulates that Internet service providers and social media should seek the consent of the parents or those exercising parental authority prior to the processing of personal information of children under 16 years of age.

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[239] *Cfr*. europa.eu/rapid/press-release_IP-16-2461_it.html.

[240] European Parliament, the EU Council. (EU) Directive 2016/680 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals with regard to the processing of personal data by competent authorities for the prevention, investigation, detection or prosecution of criminal offenses or execution of criminal penalties, and the free movement of such data, and repealing framework decision 2008/977 / JHA. Official Journal of the European Union on May 4, 2016; L191: pp. 89-131.

[241] eur-lex.europa.eu/legal-content/IT/TXT/PDF/?uri=CELEX:32016R0679&from=IT.

Particularly significant in the context of social technologies is the right to "be forgotten" provided for in the Regulations: the interested parties may obtain the cancellation of their personal data, even online, by the data controller on fulfillment of the following conditions: if the data are processed only on the basis of consent; if the data are no longer required for the purposes for which they were collected; if the data are processed unlawfully; or if the person concerned legitimately opposes their being processed. Along with the "right to be forgotten" is, the obligation of the data controller, publisher of the data, to communicate the cancellation request to all recipients processing them, as far as is technically possible. According to the Regulation, the "right to be forgotten" can only be restricted in some specific cases: for example, to guarantee the exercise of freedom of expression or the right to defence in court; to protect a public interest (e.g. public health); or when data, made anonymous, are needed for research.

Furthermore, the Regulation introduces the "right to portability" of one's personal data to transfer from one data controller to another. For example, changing email provider without losing one's contacts and saved messages.

The Regulation confirms the transfer ban on personal data to countries located outside the European Union or to international organizations that do not meet the required adequacy standards on data protection, in relation to which the Regulation introduces more stringent evaluation criteria.

Also significant for information and communication technologies is the principle of "privacy by design", whereby it is necessary to ensure data protection right from the initial stage of conception and design of a process or of a system.