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a cura di L. Palazzani

Special Issue || iCONSENT - Improving the Guidelines for Informed Consent, Including Vulnerable Populations, Under a Gender Perspective

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Editorial

Why informed consent requires attention once more?

Laura Palazzani

At the end of WWII, through an analysis of the atrocities committed by so-called doctors and men of science, the world had to face the cruel reality that torture and dehumanization had led humanity to cross lines that should never be trespassed. Trials and experiments made on prisoners without their consent -and with a masochistic level of cruelty- pushed the international community to increase the centrality of individual autonomy and the right of the patient to say "no".

Yet, despite the noble intention, individual autonomy cannot be (and has not been) the answer to all problems. At times, the (benevolent) interference of third parties (family members, doctors, spouses) might be the ethical way to go. In other situations, we might have to assess how much our consent is in fact "informed" when we thick a form online.

In addition, recent social and cultural changes in European and extra-European countries, as well as changes in technology and science, have called for more attention for informed consent. A notion in need of some restyling in line with such changes.

As a result, the European Union has decided to fund "i-CONSENT", a Horizon 2020 project aimed at improving the guidelines for informed consent so to improve the information that patients receive from clinical studies -with particular attention given towards vulnerable populations under a gender perspective.

The i-CONSENT project is first presented in this special issue of the journal by Jaime Fons-Martínez, Cristina Ferrer-Albero, Rosanna Russell, Elizabeth Rodgers, Linda Glennie, Javier Díez-Domingo. Straight after that, I illustrate the emerging ethical problems related to the presence (or absence) of informed consent in experimentation. The philosophical analysis is then carried on with the contribution by Fabio Macioce, who stresses the importance of the interconnection between autonomy and trust in all the procedures involving informed consent.

Of course, this is particular evident and sensitive with minors. For this reason, first, we have Jaime Fons-Martínez et al. analysis of the differences between the scientific literature and the legal requirements in terms of contents of the minor's assent in medical re-search. Second, Leonardo Nepi looks into the European guidelines and recommendations on minor's assent and parental permission -with particular attention on the informed consent process in paediatric clinical trials.

Minors are not the only particularly vulnerable group that our project takes into account. Women, as well as religious and cultural minorities have also much relevance in the trajectory of our investigations. As a result, Loredana Persampieri begins this part of the special issue by talking about the specific ethical -and other- challenges of gender in the conceptualization of informed consent in clinical research.

A challenge on how we might change our conceptualization of informed consent is also at the centre of Alberto Garcia and Mirko Garasic's contribution -with their article stressing the connection between neuroscience, new (possible) human rights, religion and culture.

The impact of culture and religion on informed consent is further expanded by the contribution made by me and my team at Lumsa University, where we bring forth an argument in support of new strategies for increasing participation of patients from diverse cultural and religious backgrounds in clinical trials.

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Editorial

The last two contributions are also the result of the work carried out at Lumsa University. With her paper, Margherita Daverio focuses on informed consent in translational/clinical research, paying particular attention to the ethical issues according to international guidelines. Valeria Ferro instead, takes into account the legal aspects of informed consent in clinical research -with a particular emphasis on vaccines.

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Special issue

i-CONSENT: Presentation of the Project and the Importance of Participants' Perspectives in the Informed Consent Process

Jaime Fons-Martínez, Cristina Ferrer-Albero, Rosanna Russell, Elizabeth Rodgers, Linda Glennie, Javier Díez-Domingo*

ABSTRACT: Informed consent is essential in ensuring the autonomy of participants in clinical research. However, informed consent documents are often complex and difficult to understand, and do not incorporate the patients' perspective. The informed consent process has become more focused on acquiring the participant's signature on the informed consent form, rather than being a contract that ensures the patient's autonomy through clear and complete information about all relevant aspects of a trial. The i-CONSENT project aims to improve the information that potential participants receive when deciding whether or not to join a clinical trial through the development of a set of guidelines for the informed consent process. Involving potential participants during the preparation of the informed consent and its associated materials can be a key factor.

KEYWORDS: Bioethics; clinical research; hard law; informed consent; patient participation

SUMMARY: 1. The development of informed consent – 2. The need for changes to the informed consent process – 3. Participants' opinion of the informed consent – 4. Conclusion.

* *Jaime Fons-Martínez: Fundació per al Foment de la Investigació Sanitària i Biomèdica de la Comunitat Valenciana (FISABIO). Valencia. E-mail: fons_jai@gva.es; Cristina Ferrer-Albero: Facultad de Enfermería. Universidad Católica Valencia San Vicente Mártir (UCV). Valencia. E-mail: cristina.ferrer@ucv.es; Rossana Russell: Meningitis Research Foundation. United Kingdom. E-mail: rosannar@meningitis.org; Elizabeth Rodgers: Meningitis Research Foundation. United Kingdom. E-mail: Elizabethr@meningitis.org; Linda Glennie: Meningitis Research Foundation. United Kingdom. E-mail: lindag@meningitis.org; Javier Díez-Domingo: Fundació per al Foment de la Investigació Sanitària i Biomèdica de la Comunitat Valenciana (FISABIO). Valencia. E-mail: jdiezdomingo@gmail.com.* *The article was subject to a double-blind peer review process.*
This essay is developed within the European project "Improving the guidelines for Informed Consent, including vulnerable populations, under a gender perspective" (i-CONSENT), funded by the European Union framework program H2020 (Grant Agreement n. 741856).

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1. The development of informed consent

Since the publication of the Belmont Report[1], the principle of autonomy for individuals participating in research has become a key consideration. The report highlighted the importance of informed and voluntary consent by stating that participants should be treated as autonomous entities and that those with diminished autonomy should be protected.

The Report acknowledges that the informed consent process contains three main components: information, comprehension and voluntariness. Fulfilling each of these components can however present challenges. For example, with regards to the information, for some research, complete disclosure may jeopardize the validity of the project; such as in double blind controlled trials, where neither the participant nor investigator is informed of who is receiving a particular intervention, in order to avoid study bias. Withholding such information is deemed acceptable, as long as participants are aware that some aspects of the research are not able to be revealed until the study has concluded, and that incomplete disclosure is indeed an essential requirement to fulfil study objectives, and not just a convenience factor. For the comprehension element, it is suggested that a person's capacity to understand depends on a multitude of factors including intelligence, reasoning, maturity and language. Moreover, the way in which information is presented, is considered to be as important as the content itself in enabling an individual to make an informed decision.

Participants with limited comprehension require special consideration. However, where possible these individuals should still be given the opportunity to decide whether or not to take part in research, except for when the research provides a therapy which would be otherwise unavailable: "the objections of these subjects to involvement should be honoured, unless the research entails providing them a therapy unavailable elsewhere". The Report proposes that in such cases information should also be given to a third party who is more likely to understand the potential participants' situation and is able to act in their best interest.

When the Belmont Report was published, the supervision of the principle of autonomy by independent committees, now known as ethics committees, was not required. These independent committees were however acknowledged to have an important role in assessing beneficence, and any potential risks and benefits associated with the investigation.

Informed consent is also referenced within the Declaration of Helsinki by the World Medical Association (WMA) and Guidelines for Good Clinical Practice by the International Conference on Harmonisation (ICH).

The last revision of the Declaration of Helsinki[2] mentions, in point 26, that in medical research, each potential participant must be "adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study".

[1] The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, Belmont, 1979.

[2] World Medical Association (WMA), *Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects*, Helsinki, 1964 (ed. 2013).

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It is noted that the potential participant must be informed of their right to refuse to participate in the study or to withdraw their consent at any time without any reprisal. Special attention should be given to the needs of each participant and suitable methods to deliver trial information.
The Declaration goes on to state that only after confirming that an individual has understood the information provided, should voluntary consent be obtained - preferentially in writing, although non-written consent is acceptable as long as it is formally documented and witnessed.
The Guideline for Good Clinical Practice[3] mentions:

- "4.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/favourable opinion by the IRB/IEC.
- 4.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable".

These rules highlight the oral information exchanged between the research team and the participant, and state that both oral and written information must be understandable.
The informed consent document will aim to describe all the information a potential participant needs to autonomously decide whether or not to participate in the study in simple language, using non-technical terms. However, the informed consent process has become highly regulated, and whilst vital to comply with ethical and legal standards, this has resulted in very long and complex consent documents, seen as a 'contract' between the sponsor, the researcher and the participant rather than an informative document.
Given the complexity of contracts in general, usually written by lawyers, potential participants frequently state that the oral information provided by the research team is more important than the written documents. This conflicts with ethical standards because:

1. The written information provided to the participant is not understandable and uses many medical-legal terms.
2. The oral information provided to the participant is not traceable, and is beyond scrutiny from Ethics Committees or health inspections. This is the only process within clinical trials, where no efforts are made in the traceability of information.

2. The need for changes to the informed consent process

According to international ethical guidelines by the Council for International Organizations of Medical Sciences (CIOMS) for health-related research involving humans[4], the concept of informed consent is understood as a process rather than a document. It is considered as "a two-way communicative pro-

[3] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), *ICH Harmonised Guideline. Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2).* 2016.
[4] Council for International Organizations of Medical Sciences (CIOMS), I*nternational Ethical Guidelines for Health-related Research Involving Humans,* Geneva, 2016.

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cess that begins when initial contact is made with a potential participant and ends when consent is provided and documented". These guidelines also state that "participants should be offered the opportunity to ask questions and receive answers before or during the research", extending the communicative process throughout the course of the study.

The i-CONSENT project has been developed from the perspective of this new paradigm, in which the research participant is central to the informed consent process. The objective of this project is to develop guidelines to help researchers utilise bidirectional and continuous communication during the process of informed consent, without losing sight of vulnerable populations, multiculturalism and gender perspectives. This process begins at the point of the first contact with the potential participant and continues through to the delivery of study information, discussions with the research team, the decision making process, the intervention and concludes with the follow-up after the completion of the study. Continuous communication allows for the experiences of the participant to be feedback to the research team, which can lead to improvements to the consent process in both current and future studies. The development of guidelines requires collaboration from the different parties involved in clinical trials such as sponsors, researchers and participants.

The theoretical framework of informed consent was extensively studied. Ethical recommendations[5], as well as legal norms at both a national (Spanish, German, French, British, Austrian and Italian[6]) and European[7] level were reviewed. Scientific publications on the process of informed consent in adults, in minors and from the perspective of gender and different cultures were also considered.

From the review of scientific publications, we have observed the importance of the health literacy of the population as a key element when participating in a clinical trial[8], since it allows individuals to ob-

[5] Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans. 4ª ed.* Geneva, 2016; World Medical Association (WMA), *Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects*, Helsinki, 1964 (ed. 2013); Department of Health and Human Services, *Code of Federal Regulations. Protection of Human Subjects. 45 CFR 46*, 2009.

[6] *Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los Ensayos Clínicos con Medicamentos, los Comités de Ética de la Investigación con Medicamentos y el Registro Español de Estudios Clínicos*, in *Boletín Oficial del Estado Nº 307*, 2015; *Ley 14/2007, de 3 de julio, de Investigación Biomédica*, in *Boletín Oficial del Estado, nº 159*, 2007; *The Medicine for Human Use (Clinical Trials) Regulation n. 1031/2004; Decreto Legislativo 24 giugno 2003, n. 211. Attuazione della direttiva 2001/20/CE relativa all'applicazione della buona pratica clinica nell'esecuzione delle sperimentazioni cliniche di medicinali per uso clínico; Gesetz ber den Verkehr mit Arzneimitteln (Arzneimittelgesetz - AMG), 2005; Code de la Santé Publique; Bundesgesetz vom 2. März 1983 über die Herstellung und das Inverkehrbringen von Arzneimitteln (Arzneimittelgesetz – AMG).*

[7] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials in medicinal products for human use.

[8] D.G. Scherer, R.D. Annett, J.L. Brody, *Ethical issues in adolescent and parent informed consent for pediatric asthma research participation,* in *J Asthma,* 44(7), 2007, pp. 489-496; L.R. Nelson, N.W. Stupiansky, M.A. Ott, *The Influence of Age, Health Literacy, and Affluence on Adolescents' Capacity to Consent to Research*, in *J Empir Res Hum Res Ethics*. 11(2), 2016, pp. 115-121; I.M. Hein, M.C. De Vries, P.W. Troost, G. Meynen, J.B. Van Goudoever, R.J. Lindauer, *Informed consent instead of assent is appropriate in children from the age of twelve: Policy implications of new findings on children's competence to consent to clinical research*, in *BMC Medical Ethics*, 16(1), 2015, p. 76; H. Kim, B. Xie, *Health literacy and internet- and mobile app-based health services: A systematic review of the literature,* in *Proceedings of the Association for Information Science and Technology*. 52(1), 2015, pp. 1-4; G. Quaglio, K. Sorensen, P. Rubig, L. Bertinato, H. Brand, T. Karapiperis, et Al., *Accelerating the health literacy agenda in Europe*, in *Health Promotion International*, 32(6),2017, pp. 1074-1080 (Epub

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tain, process and understand the necessary information to make an informed and autonomous health decision. In order to facilitate this process, it is necessary to provide clear and concise content which is adapted to the age and capacity of the person to whom it is addressed[9]. Efforts should be made to ensure that the potential participant has understood this information[10]. The format used to present information influences the comprehension of the information and, therefore, the format that best suits the characteristics of the participants must be used. It is recommended that technical language is avoided; that written information is simple, using short and direct phrases and where possible using pictures, photographs and / or easy to understand graphics that support the information[11].

Equally important in the informed consent process is the relationship between the researcher and the participants. Researchers should seek to establish a positive relationship with participants, which is patient-centred. They should seek to establish a climate of trust and avoid the use of non-verbal communication that suggests hierarchy. This approach promotes a socio-emotional and personal exchange that facilitates communication between the patient and the research team[12]. Researchers

2016/04/22); K. Sorensen, J.M. Pelikan, F. Rothlin, K. Ganahl, Z. Slonska, G. Doyle, et al., *Health literacy in Europe: comparative results of the European health literacy survey (HLS-EU)*, in *European Journal of Public Health*, 25(6), 2015, pp. 1053-1058 (Epub 2015/04/07).

[9] *Reglamento (UE) Nº 536/2014 del Parlamento Europeo y del Consejo, de 16 de abril de 2014, sobre los Ensayos Clínicos de medicamentos de uso humano*, 2014.; A.R. Tait, M.E. Geisser, L. Ray, R.J. Hutchinson, T. Voepel-Lewis, *Disclosing study information to children and adolescents: is what they want, what their Parents think they want?*, in *Academic Pediatrics*.18(4), 2018, pp. 370-375; E.S. Dove, D. Avard, L. Black, B.M. Knoppers, *Emerging issues in paediatric health research consent forms in Canada: working towards best practices*, in *BMC Medical Ethics*, 14:5, 2013. Epub 2013/02/01; J.N. Baker, A.C. Leek, H.S. Salas, D. Drotar, R. Noll, S.R. Rheingold, et al., *Suggestions from adolescents, young adults, and parents for improving informed consent in phase 1 pediatric oncology trials*, in *Cancer*, 119(23), 2013, pp. 4154-4161.

[10] L.R. Nelson, N.W. Stupiansky, M.A. Ott, *The Influence of Age, Health Literacy, and Affluence on Adolescents' Capacity to Consent to Research*, pp. 115-121; I.M. Hein, M.C. De Vries, P.W. Troost, G. Meynen, J.B. Van Goudoever, R.J. Lindauer, *Informed consent instead of assent is appropriate in children from the age of twelve: Policy implications of new findings on children's competence to consent to clinical research;* T.A. O'Lonergan, J.E. Forster-Harwood, *Novel approach to parental permission and child assent for research: improving comprehension*,in *Pediatrics*, 127(5), 2011, pp. 917-924. Epub 2011/04/27; S. Lee, B.G. Kapogiannis, P.M. Flynn, B.J. Rudy, J. Bethel, S. Ahmad, et al., *Comprehension of a simplified assent form in a vaccine trial for adolescents*, in *Journal of Medical Ethics*, 39(6), 2013, pp. 410-412. Epub 2013/01/26; Y. Unguru, A.M. Sill, N. Kamani N., *The experiences of children enrolled in pediatric oncology research: implications for assent*, in *Pediatrics*, 125(4), 2010, pp. 876-83; R.D. Poston. *Assent Described: Exploring Perspectives From the Inside*, in *Journal of Pediatric Nursing*. 31(6), 2016, pp. 353-365. Epub 2016/07/13.

[11] J.N. Baker, A.C. Leek, H.S. Salas, D. Drotar, R. Noll, S.R. Rheingold, et al., *Suggestions from adolescents, young adults, and parents for improving informed consent in phase 1 pediatric oncology trials*, pp. 4154-4161; D.A. Murphy, D. Hoffman, G.R. Seage 3rd, M. Belzer, J. Xu, S.J. Durako, et al., *Improving comprehension for HIV vaccine trial information among adolescents at risk of HIV*, in *AIDS Care*, 19(1), 2007, pp. 42-51; A. Twycross, F. Gibson, J. Coad. *Guidance on seeking agreement to participate in research from young children*, in *Paediatric Nursing*, 20(6), 2008, pp. 14-18; P. Grootens-Wiegers, M.C. de Vries, M.M. van Beusekom, L. van Dijck, J.M. van den Broek, *Comic strips help children understand medical research: targeting the informed consent procedure to children's needs*, in *Patient Education and Counseling*, 98(4), 2015, pp. 518-524 (Epub 2015/01/24).

[12] Y. Unguru, A.M. Sill, N. Kamani, *The experiences of children enrolled in pediatric oncology research: implications for assent*, pp. 876-83; R.D. Poston, *Assent Described: Exploring Perspectives From the Inside*, e353-

must also consider how to adapt communication and / or information in the case of minors too young to legally consent, but from whom assent is important; and pregnant women who may require special protection from risks to the foetus, using cultural mediators to aid communication with people of different cultures and / or religions[13].

3. Participants' opinion of the informed consent

To aid the development of the guidelines, a workshop was held with nine representatives of eight patient groups from five different countries (UK, Italy, Spain, Ireland and the Netherlands) and members of the i-CONSENT project team.

The workshop was focused on four themes: comprehension, patient's expectations of participation, assent in the case of minors and gender perspectives. Nominal Group Technique (NGT) was used to collect the perspectives of patient group representatives and to identify and prioritise the issues relating to the informed consent process. NGT is a highly structured, face to face technique which allows consensus to be reached in a group setting.

For each theme, the hypothetical situation of an individual participating in a clinical vaccine trial was used, and meeting attendees considered the issues relating to each theme in turn. Following NGT, attendees were asked to individually and silently generate ideas on paper, before sharing their ideas with the group. At this stage, each of the ideas were clarified and then the attendees individually ranked the issues from each of the themes in priority order.

The findings from the "comprehension" theme showed that for patients, there needs to be a clear case for their participation in a trial, involving a compelling patient story, and an appreciation of the emotional responses of patients/parents.

The clarity of the content and the format used to present information were also considered to be very important. The complexity of a sample informed consent document (read by participants before the workshop) was much criticized for the difficulty in understanding it, and this was felt to be crucial in a participant's decision on whether to participate or not.

Regarding the patient's expectations of participation in a vaccine trial, the attendees considered that the patient's understanding of the study and the informed consent process, as well as the relationship established with the research team were key factors in encouraging participation in a vaccine trial. They valued the direct benefits of participation (e.g. protection against disease from a vaccine, receiving a vaccine free of charge) and the awareness of protection against a serious illness as being important motivating factors for participation.

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e365; V.A. Miller, J.N. Baker, A.C. Leek, D. Drotar, E. Kodish, *Patient involvement in informed consent for pediatric phase I cancer research*, in *Journal of Pediatric Hematology/Oncology,* 36(8), 2014, pp. 635-640.

[13] Council for International Organizations of Medical Sciences (CIOMS), I*nternational Ethical Guidelines for Health-related Research Involving Humans. 4ª ed.* Geneva, 2016; I.M. Hein, M.C. De Vries, P.W. Troost, G. Meynen, J.B. Van Goudoever, R.J. Lindauer, *Informed consent instead of assent is appropriate in children from the age of twelve: Policy implications of new findings on children's competence to consent to clinical research*; P.E. Ekmekci, B. Arda, *Interculturalism and informed Consent: Respecting Cultural Differences without Breaching Human Rights*, in *Cultura*, 14(2), 2017, pp. 159-172.

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On the other hand, when considering factors that might discourage patients from participating in a vaccine trial, attendees considered the negative perceptions of vaccines, caused mainly by rumours, negative news stories and anti-vaccine campaigners as being the most off-putting factors. Following this, infrequent but significant risks, were also considered to be important dissuading factors, which underlined the importance of accurately communicating risk to benefit ratios.

On the theme of "assent in minors", the attendees discussed how the consent / assent process involves the minor, his/her parents and the research team. Attendees felt there was a greater need to verify the child's understanding as a possible participant in a vaccine trial, perhaps due to a heightened responsibility to protect children due to their vulnerability. Family dynamics were also considered important because the way that decisions are made within families regarding the child's participation can be influenced by social and cultural contexts. They considered that the best scenario is one in which a decision is made jointly between the child and their parents. The third issue considered in order of priority was clear and honest communication with the researcher, which should be adapted to the child's age and capacity.

The last topic was the consideration of "gender" in the informed consent process. The participants were less concerned with this issue, although some attendees favoured communication between participant-investigator of the same sex as they felt this could be more effective (for example adolescent girls may prefer to learn about a trial vaccine against a sexually transmitted disease from a female investigator). In general, they preferred not to attribute characteristics to the behaviour of men and women. The role of both individuals within a relationship were also considered, particularly in the case of a pregnant woman's decision of whether or not to participate in the clinical trial. While one participant felt that the views of both parents should be considered when a pregnant woman is involved, others felt strongly that the pregnant woman's autonomy must be prioritised, and formally consulting partners could jeopardise the rights of the woman to make decisions about her own body. Such differences in the opinions perhaps existed due to social and cultural differences among the meeting attendees.

4. Conclusion

It is recommended to involve the target population in the design of the informed consent process. The informed consent process must connect with participants from the first contact, ensuring that individuals feel their participation is relevant and significant for the research and clearly stating whether through participation, they will obtain protection against a disease.

From this first contact, a truly effective communication relationship must arise in which clear and simple information is presented, avoiding long and complicated documents with technical language and providing a balanced view of the risks and potential benefits, including comparisons with situations that are more familiar to patients. The relationship of communication with the researcher and the trust that it generates between the researcher and patient are key to decision-making and the subsequent development of the research until the end of the study. It is important to increase health literacy throughout the process, to reduce the impact of rumours and erroneous information. After

completing the study, the participant must be informed of the main results, demonstrating the importance of their participation.

In the case of minors, the ideal scenario is the group relationship between the child, his/her parents or legal guardians and the research team. Unstructured family dynamics and family hierarchy could be a barrier. It is recommended that communication is adapted to the child's age and capacity, evaluating his/her understanding and taking into account that digital media could be useful.

Gender stereotypes should be avoided and communication should be adapted to the needs of the participant.

All these aspects have been collected and taken into account in the framework of i-CONSENT project "*Improving the guidelines of Informed Consent, including vulnerable populations, under a gender perspective*" (H2020- Grant Agreement number 741856; https://i-consentproject.eu/).

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Informed Consent, Experimentation and Emerging Ethical Problems

Laura Palazzani*

ABSTRACT: Obtaining informed consent for experimentation takes on a central ethical role. This article analyses, on the basis of the historical origins of informed consent, its present role in bioethics and discusses the main ethical theories on the topic, in a pluralistic philosophical context. The author underlines the reason why informed consent should not be a detailed technical and exhaustive description of a clinical study with the exclusive aim to defend the investigators rather than protect the subjects who have been recruited. The article identifies the main ethical requirements of informed consent from the side of the researcher and of the participant, underlining the emerging ethical issues (dynamic informed consent; personalization; technological innovation; comprehension verification; physician's training in communication; health literacy for participants) and the emerging challenges (broad and flexible consent; enhanced consent; shared consent).

KEYWORDS: Bioethics; experimentation; informed consent; personalization; technological innovation

SUMMARY: 1. Informed consent and experimentation – 2. A comparison of bioethical theories: doctor/patient contract and doctor/patient alliance – 3. Ethical requirements for informed consent in experimentation – 3.1. Information as a process of empathetic communication of the doctor/researcher – 3.2. The personalization of information – 3.3. The understanding of information by the patient/research participant – 3.4. The time and ethical space of information/communication – 3.5. Assessment of the patient/researcher's competence and decision-making capacity – 3.6. Freedom of decision-making and the absence of direct/indirect inducement/coercion – 3.7. The responsibility of the researcher – 3.8. The rights and obligations of the participant – 3.9. The role of the ethics committee – 4. New modalities and challenges to improve informed consent in experimentation – 4.1. Training of the doctor/researcher in communication – 4.2. Information for the sake of education and participation (health literacy) – 4.3. The role of technological innovation in information, education and participation.

* *Full Professor of Philosophy of Law at Department of Law, Economics, Politics and Modern Languages, Libera Università Maria Ss. Assunta (LUMSA) of Rome. E-mail: palazzani@lumsa.it.* *The article was subject to a double-blind peer review process.*

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1. Informed consent and experimentation

The specific function of 'informed consent' is to provide an instrument to guarantee the doctor-patient relationship: it is an explicit expression and authorization given by the patient to accept (consent) or refuse (dissent) treatments offered by the doctor[1].

The principle of the obligation of the investigator to ask a subject to consent to participate in a clinical study after providing detailed information regarding the purposes and methods of its execution and the possible benefits and risks inherent in participation, was introduced in 1947 from the Nuremberg Code. It derives from the sentence that the International Tribunal issued in that city on 19 August 1947 at the end of the trial against the Nazi doctors who had carried out criminal experiments in concentration camps on prisoners of war as well as women, children and persons with disabilities in a state of total unawareness[2]. This principle was later accepted by the 18th World Medical Association General Assembly held in Helsinki in 1964 in the Declaration of Helsinki (and subsequent revisions), which constitutes the ethical code of the researcher. While the Nuremberg Code still left the request for consent within the context of the direct deontological relationship between doctor and patient, the Declaration of Helsinki introduced for the first time the principle of the need for an additional external guarantee provided by the oversight of an independent committee, responsible for examining the study protocol and possibly providing feedback and suggestions to the investigator.

Even in subsequent documents, from the development of guidelines on clinical practice of the Council for International Organizations of Medical Sciences (*International Ethical Guidelines for Biomedical Research Involving Human Subjects*, adopted in 1993 with subsequent revisions) to *Good Clinical Practice* approved by the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use in 2002 to the documents with importance at International and European level, binding to varying degrees. (*Charter of Fundamental Rights of the EU,* 2000, Article 3, Council of Europe, *Convention on Human Rights and Biomedicine,* 1997, Article 5 and *Additional Protocol concerning Biomedical Research*, 2004, UNESCO, *Universal Declaration on Bioethics and Human Rights*, 2005, Article 6, *the European Union Regulation* No. 536/2014 of 16 April 2014 on the clinical trial of medicinal products for human use, which repeals Directive 2001/20/EC), which today constitute the main regulatory reference for experimentation on humans, make explicit reference to informed consent.

Above all, it is in the field of human experimentation that informed consent has a particularly important role to play. Experimentation is essential in the context of scientific research to advance knowledge for the possible treatment of diseases. The purpose of experimentation is in itself good, as it aims to improve the conditions of human health and well-being, but the constitutive uncertainty (experimentation means 'trying' or 'testing'), the difficulty in quantifying and predicting *a priori* the possible risks balancing them with respect to the desired benefits, the certainty or probability that

[1] In clinical practice, informed consent is required with regard to treatments (for diagnosis, therapy, rehabilitation) that have a certain degree of invasiveness on the body, and is considered implicit in cases of non-invasive treatments.

[2] R.R. FADEN, T.L. BEAUCHAMP, *A history and theory of informed consent*, New York, 1986. R.R. FADEN, T.L. BEAUCHAMP, *The concept of informed consent,* in T.L. BEAUCHAMP, L.WALTERS, J.P. KAHN, A.C. MASTROIANNI (Eds.)*, Contemporary issues in bioethics*, 7th ed., 2008, pp. 166–170.

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the benefits for the subject involved in the experimentation may not be direct, but only indirect, or even only probabilities projected into the future, make this practice full of problematic elements that require adequate moral reflection, in order to protect human beings, their dignity and fundamental rights[3].

It is between the radical techno-scientism of a libertarian and utilitarian kind, which pushes towards experimentation 'at any cost', with a technophilic blind faith and optimism in the benefits, and extreme anti-scientism, which blocks and obstructs research in a pessimistic and technophobic manner for fear of the negative effects, that bioethical reflection has consolidated a shared stance on certain limits of licitness in human experimentation. Although the context of constitutive moral pluralism in the bioethical debate continues to give rise to theoretical discussions and various practical interpretations, reflection on human experimentation has developed some common lines, at the bioethical and bio-legal levels, allowing for the configuration of a national and international legislative framework of reference (both soft law and hard law) with some common ethical principles and criteria, deemed particularly important in the context of human experimentation. Informed consent is, specifically, among these criteria.

When reference is made to informed consent, we generally think of a document drawn up in written form that presupposes and implies the precise modalities of the relationship between doctor and patient: the doctor has the duty to inform the patient about experimental treatment; the patient has the right to be informed and express (or not express) consent to the medical act[4]. Information is the condition for the structural possibility of consent: without information, consent is not possible. Consent is the condition for the structural possibility of experimentation: without consent and against consent the researcher cannot conduct experiments.

Historically, the ethical requirement for informed consent has arisen from events that shed light on experimentation carried out only for the good of science but 'against' human beings, human beings not being adequately respected in their dignity, used in an unconscious way only as a means and not also as an end. The experiments of Nazi doctors were an extreme historical example, like other events, which stimulated the birth of bioethics.

2. A comparison of bioethical theories: doctor/patient contract and doctor/patient alliance

The binomial “information/consent” is used in different ways according to the model of medicine and concept of ethics which it makes reference to. Informed consent marks a shift from a 'paternalistic' model of medicine to a model which values patient autonomy. Paternalism was an authoritarian model of medicine which considered the doctor to be the depository of knowledge, being in a position of dominance/power and superiority, while the patient was placed in a position of subjection and inferiority. In accordance with this perspective, the doctor decided 'for' the patient, imposing his/her will without offering explanations, without listening to the needs and desires of the patient,

[3] Italian Committee for Bioethics, *Drug experimentation,* 1992. Unesco International Bioethics Committee, *Report on informed consent*, 2008.

[4] If the right not to be informed is foreseen in the informed consent related to clinical practice, this right does not exist in experimentation.

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ignoring inclinations and subjective perceptions. This model, at least in Western societies, is criticized on the ground that the doctor does not have arbitrary dominion over the patient's life and health and that the patient is not merely a passive instrument, but an active subject who must participate and be involved in a fully informed way in the decision.

The paternalistic model is opposed to the 'contractual' model that considers the doctor and the patient to be moral agents and free contractors. This model of medicine falls within a liberal-libertarian concept of bioethics, which on a non-cognitivist basis (the assertion that objective truth is not knowable) as well as on an individualistic basis (the affirmation of free subjective decision even in relation to moral values), believes that patient self-determination, whatever that may be, must be placed at the centre.

In this perspective, the doctor must inform the patient in a detailed and neutral manner, limiting himself/herself to presenting the range of alternative options, leaving the autonomy of choice to the patient or, if anything, helping the patient to interpret the best choice consistent with his/her beliefs (all deemed to be acceptable, in an equivalent manner). It is an impersonal model, which reduces the doctor to health counsellor and the patient to user, resulting in the overthrow of paternalism, attributing a prevalence to the patient's will and reducing the doctor to passive executor of the will of others. In this sense, contractual medicine re-proposes a unilateral and hierarchical model (analogously to paternalism), overturning its parts. On a contractualist view, consent is understood as a merely formal procedure for registering the patient's self-determination (whatever it may be).

This view of informed consent has been subjected to criticism, grounded, on one hand, in the supposedly unreal assumption of symmetry between doctor and patient or in the abstract condition of full mental clarity and self-referentiality of the patient in the decision, and on the other, in the unavoidable trend towards the shunning of therapeutic responsibility on the part of the doctor and the drifting towards a medicine known as “defensive medicine or defensive medical decision-making”. In this direction, a change in the meaning of informed consent would be introduced with respect to its original meaning, leading the doctor/researcher to act or not act in his/her own interest and not in the interest of the patient, in order to prevent accusations of *malpractice* and consequent legal sanctions.

In contrast to paternalistic and contractualist medicine, there are several lines of thought upholding the key importance of dialogue and the relational dimension, precisely in informed consent, recognizing - albeit the patient's constitutive asymmetry in relation to the doctor, given the former’s position of scientific incompetence and vulnerability in sickness - a 'therapeutic alliance' or 'therapeutic relationship' that is outlined in the personal encounter and common commitment to health care.

According to the relational model of therapeutic alliance, information does not end with the description of the facts, but it integrates with counselling in the form of advice that urges the patient to become aware of problems, to elaborate a reasoned and not an emotional choice, facilitating a decision-making process through dialogue as a dialectical and communicative interaction, aimed at identifying a common goal. This model places the patient at the centre as a person, considered in his/her dignity *per se*, and supports the ethical duty as well as the deontological duty of the doctor to treat and care for the sick person and respective fragility, especially in the context of experimentation, within the development of scientific research, given the condition of uncertainty in the benefit-risk

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balance. It is in this context that the bioethical relevance of the Hippocratic paradigm strongly re-emerges: it is a matter of acknowledging that the relationship with the patient is a structural part of the medical act and of the experimentation itself[5].

The individual, whether healthy or sick, male or female, adult or minor, whatever the cultural affiliation or concept of religion, who freely participates in research is not a mere object manipulated or used as a tool to accomplish goals that are to him or her unknown. Ideally, this is an individual who cooperates in solidarity to the improvement of medical treatment and to the progress of scientific knowledge that will have possible future benefits for mankind.

In this sense, informed consent is therefore a fundamental ethical requirement in experimentation; it expresses, on one hand, the therapeutic responsibility of the researcher towards the subject and, on the other, it develops a broader participation of the patient in the decisions concerning him/her. It cannot and must not be reduced to a mere "form" to be filled out with indifference by the researcher and hastily "signed" by the subject, in order to comply with purely bureaucratic requirements. A form of this kind, even if carefully prepared, could never cover all the unpredictable situations related to the experimental-clinical reality and risks impersonally proceduralising the relationship and distorting the relational and interpersonal constitutive meaning of informed consent, which is aimed at protecting the health of the subject.

In the field of bioethical reflection, both in scientific discussion and in the deliberations of international, European and national bioethics committees, several 'ethical requirements' have been elaborated, and are explicitly being refined, which set out the conditions for a practical implementation of informed consent, being more consistent with its original authentic meaning in the relational-dialogical context[6].

3. Ethical requirements for informed consent in experimentation

The existence of the patient's informed consent is not in itself sufficient to make a study "ethical": it is also a matter of verifying 'how' informed consent is given. The informed consent form *is a neces-*

[5] This is the stance of the Italian Committee for Bioethics: "The legitimation and basis of medical treatment is, at the same time, an instrument to realise the search for a therapeutic alliance - within the law and deontological codes - and the full humanisation of the doctor and patient relationship, to which today's society aspires"; "The information is aimed not at filling the inevitable gap in technical knowledge between doctor and patient, but at placing a subject (the patient) in the condition to carry out his or her rights in a correct way and hence to express a will that is in fact his or her own; in other words, to put him or her in the situation to choose" (ITALIAN COMMITTEE FOR BIOETHICS *Information and consent related to medical acts,* 1992).

[6] J.W. BERG, P.S. APPELBAUM, C.W. LIDZ, A. MEISEL, *Informed Consent: Legal Theory and Clinical Practice*, 2nd ed, New York, 2001. P.J. CANDILIS, C.W. LIDZ, *Advances in informed consent research*, in F.G. MILLER, A. WERTHEIMER (Eds.), *The Ethics of Consent: Theory and Practice*, New York, 2010; J. KLEINIG, *The nature of consent*, in F. G. MILLER, A. WERTHEIMER (Eds.), *The Ethics of Consent: Theory and Practice*, New York, 2010; N.C. MANSON, O. O'NEILL, *Rethinking Informed Consent in Bioethics*. Cambridge, 2007.

sary but not sufficient element, if it is not accompanied by fundamental requirements[7]. The elements of ethically authentic informed consent are[8]:

3.1. Information as a process of empathetic communication of the doctor/researcher

Information from the doctor/researcher and the healthcare team (on the aims of the study, methodology, risks and benefits, alternatives, revocability of consent, privacy protection) must be correct and scientifically and technically comprehensive, as well as informative and understandable, without becoming too superficial. Excessive technicality, on one hand, and excessive simplification, on the other, do not allow the subject to gain a proper understanding.

Information must not be the mere technical and cold transmission of data and news in a detailed way, but it must redress the inevitable difference in knowledge between researcher and research participant, placing the subject in a position not only to receive information but also broaden knowledge and gain awareness. In this sense, information is and must also be a *dynamic process* of interpersonal communication, which is achieved through the modality of interaction between doctor/researcher and patient/research participant, certainly not reducible to a single encounter but achievable through a regular, constant and continuous relationship, called for by the doctor/researcher and requested by the patient/research participant, in order to create a relationship of trust suitable to facilitate communication. It is seldom possible to provide full information in a single meeting[9]. A new consent is indispensable, especially if the research continues in different directions.

Communication must also be *humanly sensitive*, ethically aware with regard to sick subjects, who face uncertainties and risks in participating in research. Information calls for a substantial understanding of the experiences, hopes and fears of those who suffer and therefore the doctor/researcher is required to possess and cultivate certain human qualities or empathic virtues (the ability to listen and dialogue, psychological sensitivity, the trait of delicacy) which enable them to perform their professional duties giving special attention to the subject, who must always have a central role.

It is necessary to reconcile the subject's right to know what participation involves in terms of potential benefits and risks with the amount of available knowledge (which is often scarce in the early stages of development of a new drug) and with the patient's real possibility of understanding, and avoiding fuelling unjustified and excessive/unreasonable expectations or unnecessary anxieties and fears in the subject, not commensurate with the real benefits and risks.

[7] President's Commission For The Study Of Ethical Problems In Medicine And Biomedical And Behavioural Research, *Making Health Care Decisions: A Report on the Ethical and Legal Implications of Informed Consent in the Patient-Practitioner Relationship*. Washington, D.C., 1982.

[8] C. Grady, *Enduring and emerging challenges of informed consent*, in *The England Journal of Medicine*, 26, 2015, pp.855-862.

[9] S. Joffe, R.D. Truog, *Consent to medical care: the importance of fiduciary context*, in F. G. Miller, A. Wertheimer (Eds.), *The Ethics of Consent: Theory and Practice*, New York, 2010. F. G. Miller, *Consent to clinical research*, in F. G. Miller, A. Wertheimer (Eds.), *The Ethics of Consent: Theory and Practice*, New York, 2010. F.G. Miller, A. Wertheimer, *Preface to a theory of consent transactions: beyond valid consent*, in F.G. Miller, A. Wertheimer (Eds.), *The Ethics of Consent: Theory and Practice*, New York, 2010.

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3.2. The personalization of information

Informed consent must not be reduced to a standard form with few variations depending on the context, instead, it should be thought out in an appropriate manner (tailored consent) with regard to the different specific needs of patients and subjects, or at least of homogeneous groups of patients.
The theory of the "reasonable person standard"[10] (distinct from professional practice and the patient's subjective standard), that is, assuming a reasonable standard person as a useful model adaptable to the prevailing circumstances in which a reasonable person can find himself/herself, is difficult to apply in specific situations of particular vulnerability or cultural difference.
There is increasing awareness, in bioethical and bio-legal reflection, of the need for specific attention to be paid to the differentiation of subjects on the basis of age (minors, the elderly), sex (men, women during fertility, pregnancy, breastfeeding), ethnic group (according to cultural and/or religious diversity), conditions of awareness in relation to pathologies that compromise *consciousness* (e.g. people with dementia), emergency conditions (we talk about deferred consent).

3.3. The understanding of information by the patient/research participant

Information must be neither excessive nor minimal, but sufficient for the patient/research participant, and above all it must be *fully understood*. The information communicated to the subject must make him/her aware of the significance of the experimentation and what participation actually entails (also in terms of commitment and responsibility) and verify the subject's critical awareness of the potential/possible benefits and risks, as well as the possible consequences of non-participation. It should also be considered that understanding involves not only the rational and intellectual dimension, but also the emotional dimension, connected to individual psychological experience closely related to the pathology.
To ensure the conditions of understanding, it is essential that the information/communication is "adapted" to the specific needs of subjects, with reference to age, sex, cultural and/or religious affiliation. The appropriateness and adequacy of the information is to be evaluated *case by case*, based on the existential, social and cultural context.
It is obviously difficult to say whether it is possible to define the universal characteristics of a "reasonable man" and the breadth of information that he/she would like to receive. It is more logical to think that information must be adapted to the individual subject or at least to groups of subjects, taking into account the numerous personal, social and cultural factors.

3.4. The time and ethical space of information/communication

Information must be provided in a suitable place for communication and the subject must be given adequate and sufficient time to reflect on the contents of the information and decide whether to participate in the study, in *situations of no urgency*.

[10] R.R. FADEN, T.L. BEAUCHAMP, *The concept of informed consent,* cit., pp. 166-170. J.D. MORENO, A.L. CAPLAN, P. ROOT WOLPE, *Informed consent*, in R. CHADWICK (Ed.), *Encyclopedia of applied ethics*, Vol. 2, London/ Sydney/New York, 1998, pp. 687-697.

Informed consent in this sense should also become the place and time of communication and education of the patient to make conscious and responsible choices regarding his/her own health and collective health.
Obviously in cases of emergency, the lack of time for information and communication is to be respected. In these cases, informed consent is unethical; the only possible solution is deferred consent.

3.5. Assessment of the patient/researcher's competence and decision-making capacity

The subject must be in the physical-psychic-social and cultural conditions to be able to decide in a conscious and personal way. Being under age, having a physical and/or mental illness, being in a particular social-cultural condition are factors that can affect the concrete ability and aptitude to make a particular decision. The decision-making competence of a subject should therefore be verified on an individual basis, before, during and after a decision concerning experimentation that is deemed to be significant, particularly those experiments encompassing greater risks and uncertainties.
In order to recognize the capacity of a subject, it is important to examine how the deliberative process takes place. By virtue of this criterion, it is necessary to ascertain whether the subject is truly able to communicate with the doctors, showing outward signs of having understood the information and being ready to decide, with an understanding of the alternatives and their related nature, (alternatives that must be envisaged without the encumbrance of operant conditioning) as well as providing responses endowed with coherence, and persisting in the conclusions expressed.

3.6. Freedom of decision-making and the absence of direct/indirect inducement/coercion

For informed consent to be valid, it must be freely expressed, as far as possible. Freedom with which a subject adheres to a proposal to take part in experimentation can be subjected to external influences and pressures, and at times downright direct/indirect coercion coming from the family or social context, facilities, researchers, sponsors, even through incentives. One of the forms of direct incentive can be given by payment or compensation for the risk taken: this modality is not ethically acceptable, because it would make adhesion to research not authentic. The very statement that those who participate in the study will receive more attention from the doctor or researcher and better opportunities for consideration/treatment, constitutes an 'indirect incentive', especially for particularly vulnerable persons, such as minors, pregnant women, immigrants.
In order to guarantee the free voluntariness of participation, it is essential to exclude relationships of dependency or hierarchy between investigator and research subject that could result in a possible element of psychological coercion. However, it cannot be denied that a patient has a strong psychological dependency on the doctor treating him: patients expect from their doctors a recovery or at least relief from their suffering. Faced with the request to participate in a study, it is inevitable that the patient may fear upsetting the person who is responsible for his/her health and, therefore, the patient can feel somehow obliged to accept.
As a matter of fact, investigations carried out on patients who had participated in clinical trials have shown that the fear of displeasing the doctor, or in any case undermining confidence in their proposals, had been a determining factor in accepting to participate in a very high number of cases, while the real understanding of the study was scarce or had weighed very little on the decision. It is

therefore incontrovertible that in obtaining valid informed consent, a correct and transparent relationship between patient/research subject and doctor-researcher remains the basic element. However, the revocability of consent without adverse consequences for patient care and the possible discontinuation of experimentation for justified reasons by the researcher should always be made explicit.

3.7. The responsibility of the researcher

Researchers should not forget that the personal integrity and well-being of the subjects in the study fall within their main responsibility. The researcher's responsibility must be proportionate to the research risk.
However, the obligations of the researcher towards the research subject are not limited to providing information and obtaining consent. He/she must also, on a regular and continuous basis, share with the subject the data and facts that come to his knowledge during the course of the study, which could modify the subject's willingness to continue to participate (for example: toxicological test results, major adverse events, doubtful therapeutic effects).
The doctor may have a double role: as both treating physician and researcher, with the ensuing possibility of a conflict between ethical obligations, both to treat patients with the treatments he/she considers most appropriate, as well as to perform his/her work with methodological and scientific correctness, in order to contribute to the progress of knowledge. No doctor/researcher should agree to participate in a trial where he/she is required to administer a treatment he/she deems harmful. Doctors/researchers should immediately suspend a study if they are convinced that it is harmful to patients/research subjects[11].

3.8. The rights and obligations of the participant

Informed consent must explicitly clarify the rights and guarantees to protect research subjects, notably the right to refuse to participate and the right to withdraw from a clinical study, at any time, without any resulting detriment and without having to provide any justification. Research participation must be understood as a commitment by the participant who, despite the possibility of revocation, is obliged to meet research conditions, to show loyalty to the researcher. The possibility of discontinuation of the research by the researcher must be made clear and explained.

3.9. The role of the ethics committee

Therefore, the moment in which the relationship between doctor/researcher and patient/research subject also assumes aims of general interest that go beyond the advantages of the single individual, it is inevitable to feel the need for an external, public guarantee, constituted by a third impartial actor, who is the expression and guarantor for the behaviour of the doctor/researcher towards the patient/research subject and the consent of society.

[11] The choice of randomization is particularly complex; this method of experimentation seems in fact incompatible with the possibility of providing the patient/research subject with complete information and therefore of acquiring informed consent. The question becomes even more difficult in the case of comparison with placebo, which is also considered of crucial importance for the evaluation of the pharmacological effect.

This is the concept of "renewal of consent" which expresses the oversight that an Ethics Committee must exercise on the progress of the study, in order to verify that the judgment of ethicality and feasibility given at the beginning does not undergo modifications during conduct of the clinical study.
The recourse to the patient's signature or that of one or two witnesses and approval of the informative material by the Ethics Committee represent the tools that should provide public guarantee that a fair balance between the factors mentioned has been achieved. A copy of the informed consent must always be given to the subject.

4. New modalities and challenges to improve informed consent in experimentation

4.1. Training of the doctor/researcher in communication

Researchers must be able to inform, and at the same time possess sufficient capacity for psychological introspection and empathy, as mentioned above, to enable them to adequately address a variety of complex situations, adapting the communication to the specific condition of research subjects. In order to verify the latter's understanding and effective decision-making capacity, to identify whether consent is given with full conviction and awareness, a capacity, in addition to technical and scientific competence, is required by the doctor/researcher: it presupposes also the willingness to listen, dialogue, and empathize.
The acquisition and development of this skill requires adequate educational programs, even specialized ones, with respect to particular situations that allow doctors/researchers to pursue the goals of their profession and build the therapeutic relationship on trust and mutual respect, beyond specialist fragmentation, so as to allow the recovery of a holistic vision of the patient/research subject, moving beyond technical competence towards human receptiveness.
In this context, there is also the need for the doctor/researcher, who is oriented towards clinical research activities, to receive adequate training in the field of bioethics, aimed at fostering the values of personal relationship with the patient/research subject and allowing the doctor/researcher to understand the authentic meaning of informed consent beyond the merely formal and procedural dimension.

4.2. Information for the sake of education and participation (health literacy)

Proper reception of the information that the doctor/researcher has to convey, requires a level of cultural competence of the patient/research subject that not all subjects necessarily have. In addition, research participants often have to make decisions in difficult psychological conditions, on a personal level, and in these cases not even cultural and/or scientific preparation can be sufficient to use the information received, in order to develop appropriate choices.
The decision to offer patients/research subjects all available information, can hinder or even block the ability to choose, because it may induce in them defensive attitudes when faced with what may seem the prospect of risk, or patients can be induced to demonstrate and experience symptoms or illnesses generated only from knowing of their possibility.
In this sense, the doctor/researcher must know how to assess the quantity and quality of the information to the patient/research subject, tailoring it to the patient/research subject's cultural level,

trying to communicate the information by inserting it in the context of health training and education of the patient (health literacy).
This is an aspect that is becoming increasingly important in our society, due to the emergence of the patient's *responsibility* towards his/her own health[12] and the subject's increasingly essential *participation* in health[13].

4.3. The role of technological innovation in information, education and participation

The latest technological developments can play a substantial and decisive role in the innovation of informed consent methods, to facilitate the process of information, education and participation of the subject.
Within the context of the most recent techno-scientific developments, characterized by the speed and dynamism of the evolution, medicine is also changing. There is talk of a new paradigm of medicine: the so-called 4/5 'P' medicine, or preventive-predictive, personalized, participatory, precise medicine[14]. Medicine is geared to the citizen, with precision as regards the individual, and with an active direct involvement in knowledge. In the era of 'data intensive medicine', in the context of so-called *'big data'*[15] (expression that indicates the enormous quantity of information that can be collected at an increasingly fast speed, also in the field of medicine and health thanks to the developments of the "omics" sciences)[16], new challenges emerge for informed consent, which is beginning to take on new configurations[17].
New technologies can help the researcher to facilitate *communication and understanding* for those belonging to a lower socio-cultural level. Technologies can contribute, through the use of video or animation, to the possibility to grasp concepts and simplify the transmission of complex content through images, diagrams, figures. In this way, information can be more easily adapted to the specificity of the patients, based on their ability to understand.
Furthermore, technologies can offer *tools to verify and ascertain the effective understanding of patients.* The evaluation of the "receptivity" of the patient to the informative talk is generally entrusted to the sensitivity and experience of the doctor. It would be important to have technologies available to help the doctor to verify genuine understanding.

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[12] UNESCO, INTERNATIONAL BIOETHICS COMMITTEE, *Report of the International Bioethics Committee of UNESCO (IBC) on social responsibility and health*, 2010.
[13] EUROPEAN GROUP ON ETHICS IN SCIENCE AND NEW TECHNOLOGIES (EGE), *New health technologies and citizen participation*, 2015.
[14] M. FLORES, G. GLUSMAN, K. BROGAARD, N.D. PRICE, L. HOOD, *P4 Medicine: how systems medicine will transform the healthcare sector and society,* in *Personalized* Medicine, 10 (6), 2013, pp. 565-576. Medicine understood in this way has the objective of analysing individual variability in the relationship between genetics and the environment, with reference to the biography of the individual and lifestyle and increasing the effectiveness of treatments, reducing the risks in taking a specific drug.
[15] The 'volume' indicates the enormous amount of data; 'speed' refers to acceleration in data generation and data processing; the "variety" highlights the heterogeneity of the sources (computers, mobile phones, internet, sensors and mobile devices); the "veracity" underlines the possible authenticity of the data. The "value" of the data should also be added, understood as the relevance and significance in the current context.
[16] ITALIAN COMMITTEE FOR BIOETHICS, *ICT, big data and health: ethical considerations*, 2016.
[17] N.C. MANSON, O. O'NEILL, *Rethinking informed consent in bioethics*, Cambridge, 2007.

In addition, technologies can improve the *participation* of the subject in the research, through the availability of ICT platforms that provide informative material to research participants, allowing them to maintain continuous contact with the subjects in an interactive way (offering information and receiving information, being able to provide updates to subjects, modify or confirm participation in the research) and share research results with them *(benefit sharing*). This allows for the so-called *'empowerment*' of research subjects, increasing their knowledge and information (so-called *enhanced consent*) and their active participation, and it equally enables constant monitoring of the research (both by the doctor and participant), as well as pharmacovigilance during and after the study and social dissemination of results.

In this way, it is the individual himself/herself who can choose the level of complexity of the explanations and information (*tailored consent*); consent adapts to the preferences of the subject, including also the possibility to choose the type of consent preferred (broad or limited). It is the possibility to inform and educate the subject/patient to understand the paths of the research and to have the, continuously updated, tools of comprehension to be able to make an informed decision, to tackle disinformation and unconscious decisions. The opportunity for *shared consent* also opens up (sharing consent): with participation and co-sharing, or the interactive and reciprocal sharing of research results with other subjects/patients, in the same condition, and all those who may derive benefit from them. Aware of the fact that there are risks for privacy and confidentiality in giving and sharing data.

In this context, there is an emerging ethical need for digital users to control data management in general and health data in particular, in a transparent manner. Who is collecting and who will use the data, what data, how are they collected, where are they stored, for how long, for what reason and purpose (health and/or commercial purposes) should all be clearly specified, together with the possibility of revocation without negative consequences, rectification or integration or deletion of data (so-called 'right to oblivion' or right to cancellation, the right to be ignored/forgotten).

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Special issue

Informed Consent Procedures Between Autonomy and Trust

Fabio Macioce*

ABSTRACT: Informed consent has been implemented through a set of rules, at both national and international level, which protect individual autonomy as much as possible from paternalism, abuse, inducement, mistreatment, and deception. However, informed consent must not be merely understood as the outcome of a procedure for the transfer of information, however precise and detailed it may be. The article advocates its being rethought within a relational perspective, according to which not only the quantity or the quality of the information provided is at stake, but also the relational context within which this information is developed. The precondition for free and informed consent, besides the information received, is the relationship of trust between the parties involved, and the consistency between their modes of interaction and the need to maintain mutual trust. In that sense, the information is adequate and relevant not in itself, but as a function of the kind of relationship between the parties.

KEYWORDS: Autonomy; relationship of trust; informed consent; communication; decision-making process

SUMMARY: 1. Introduction – 2. Informed consent and autonomy: the relational dimension – 3. Relational autonomy and trust – 4. Informed consent and trust – 5. Rethinking informed consent: some remarks – 6. Conclusion.

1. Introduction

In the literature, significant consideration has been devoted to the relationship between autonomy and trust, and even more to the problem of the relationship between autonomy and informed consent[1]. However, less consideration has been given to the problem of the relationship between informed consent and trust, and above all to the question of how to model informed consent procedures so that the expression of consent is not a procedural alternative to fiduciary relationships. Rather than being a sort of inevitable surrogate of these relationships, informed consent

* *Full Professor of Philosophy of Law at Department of Law, Libera Università Maria Ss. Assunta (LUMSA) of Palermo. E-mail: fmacioce@libero.it.* *The article was subject to a double-blind peer review process.*
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[1] See R.M. VEATCH, *Autonomy's temporary triumph*, in *Hastings Center Report*, 14 (15), 1984, pp. 38-40. R.R. FADEN, T.L. BEAUCHAMP, *A history and theory of informed consent*, Oxford, 1986. T.L. BEAUCHAMP, *Autonomy and Consent*, in F.G. MILLER, A. WERTHEIMER (eds.), *The Ethics of Consent: Theory and Practice,* Oxford, 2010, p. 57. F.G. MILLER, A. WERTHEIMER (eds.), *The Ethics of Consent: Theory and Practice,* Oxford, 2010.

procedures should be the regulatory context within which the subject's autonomy is guaranteed, and the outcome of a relationship that fosters both interpersonal trust (between patient and physician) and systemic trust (towards institutions and health authorities).

For this purpose, it is necessary to rethink both the methods and the content of informed consent procedures, so as to tailor them to the person who is asked to express consent, also considering the specific situation in which such information is to be given. In other words, we need to go beyond the model in which some information is abstractly relevant, and a certain (pre-determined) amount of information is necessary, in order to adopt a perspective in which both the information and the way of giving or explaining it differ from person to person, according to their specific vulnerabilities and needs.

However, although desirable it may be to tailor the procedures of informed consent to the needs of the individuals involved, this objective clashes with a number of difficulties of various kinds. Among them, there is a theoretical difficulty (unrelated to practical, economic or individual factors) deriving from the fact that, for understandable reasons, it is inevitable that informed consent is incorporated (and therefore made evident) in documents with legal value: therefore, in necessarily formal, standardized, and pre- determined documents.

The asymmetry of power and knowledge between the provider (researcher or doctor) and the subject (patient or research participant) requires that both parties involved in the procedure be guaranteed, first of all, from a legal point of view. Renouncing to such guarantees, and simply relying on the trust relationship between patient and doctor, is unrealistic. Notwithstanding this, it is possible to ensure that informed consent is not simply an agreement between the parties for the guarantee of mutual rights, but it is able to implement, and display, the relationship of trust between them.

My concern, and the purpose of this paper, is to argue that informed consent procedures should take the relational character of autonomy into consideration, as well as the link between informed consent, autonomy and trust. In so doing, one might protect the exercise of personal autonomy, rather than its mere possibility, therefore fostering trust between the subjects involved, as well as in the whole health care system. For this purpose, it is necessary to take into consideration the asymmetry of power and information among the subjects involved, and make it the basis of an asymmetrical distribution of burdens: information providers must give evidence that they have taken due account of the specific vulnerabilities and needs of the person expressing consent, through appropriate choices of communication methods and contents.

In order to discuss these aspects, I will briefly highlight the relationship between informed consent and autonomy, with specific regard to the relational dimension of autonomy; then, I will focus on the interplay between autonomy, trust, and consent; finally, I will discuss how the procedures for informed consent should be adapted, so as to be more suited to managing the relational dimension of personal autonomy and fostering trust, at both an interpersonal and intra-personal level.

2. Informed consent and autonomy: the relational dimension

It has been argued, with compelling reasons, that the pivotal role of informed consent is linked to the overcoming of the paternalistic model of the medical encounter, which for centuries had been un-

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derstood as necessarily asymmetric[2]. Therefore, informed consent may be understood as having two different meanings, both linked to the concept of autonomy[3]; in a first sense, informed consent is the act whereby an individual with substantial understanding, and in the absence of control by others, intentionally authorizes a medical intervention or participation in research. In a second sense, it is a form of legal authorization, that is, an authorization determined by prevailing social rules, like in the cases of minors or other people not able to give their consent[4]. In both cases, informed consent expresses authorization: in the first case, it is determined by an autonomous chooser, who acts intentionally, with understanding, and without any controlling influence on his/her own behalf; in the second case, the person's wishes are expressed by others, according to social and legal provisions, due to the person's lack of understanding and consequent incapacity to give consent.

Over recent years, such a connection between informed consent and autonomy has been the subject of an enormous amount of criticism, aimed at stressing its inability to balance individual and public interests, and its inefficacy in the cases of patients with impaired capacity, psychiatric patients and in end-of-life situations; moreover, its ambiguity has been stressed along with its tendency to conceive the body as property, as well as the shortcomings of such an understanding in specific sectors, such as genetics and the managing of genetic data[5].

In addition, the focus on personal autonomy has been deemed to be misleading, since it does not take the social, economic and personal factors of vulnerability seriously into consideration. In these cases, and in similar ones, the exclusive reference to the principle of autonomy may be counterproductive, as it entails the risk of increasing people's vulnerability rather than reducing it. For this reason, a different understanding of autonomy is necessary, one which does not stem from a hyper-individualistic conception.

Such a different model of subjective autonomy is more consistent with the intersubjective dimension of human life. The notion of autonomy is understood not as a subjective predicate (a quality of individuals, due to which we may say that Paul is autonomous and Peter is not), but as an ontological feature whose exercise is facilitated or inhibited by many factors: among these factors, the interpersonal networks available for any person are of paramount importance. In this sense, any person is autonomous, even if some do need the support of others to exercise their autonomy, or a stronger support than others[6].

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[2] See *Ibidem*. See also P. Borsellino, *Informed Consent. Some Philosophical-Legal Concerns*, in *Salute e Società*, XI (3), 2012, p. 22.

[3] See T.L. Beauchamp, *Autonomy and Consent*, cit., p. 57.

[4] See *Ivi*, cit., p. 59. R.R. Faden, T.L. Beauchamp, *A history and theory of informed consent*, Oxford, 1986.

[5] See R.M. Veatch, *Autonomy's temporary triumph*, in *Hastings Center Report*, 14 (15), 1984. P. Benson, *Autonomy and Oppressive Socialization*, in *Social Theory and Practice*, 17, 1991, pp. 19-35. O. O'Neill, *Autonomy and Trust in Bioethics*, Cambridge, 2002. J. Anderson, J. Christman. (eds.), *Autonomy and the Challenges of Liberalism. New Essays*, Cambridge, 2005.

[6] See M. Friedman, *Autonomy and the Split-Level Self,* in *Southern Journal of Philosophy*, 24, 1986, pp. 19-35. M. Friedman, *Autonomy in Social Context,* in C. Peden, J.P. Sterba (eds.), *Freedom, Equality, and Social Change*, Lewiston, NY, 1989, pp. 158–69. D.T. Meyers, *Self, Society and Personal Choice*, New York, 1989. C. Mackenzie, N. Stoljar, *Autonomy Refigured*, in C. Mackenzie, N. Stoljar (eds.), *Relational Autonomy: Feminists Perspectives on Autonomy, Agency, and the Social Self*. New York, 2000. J. Anderson, *Autonomy and the Authority of Personal Commitments: From Internal Coherence to Social Normativity*, in *Philosophical Explorations: An International*

For these reasons, autonomy largely depends on the resources available for the individual, as well as on institutional facilities and legal instruments that make it possible to exercise it. Among these facilities and instruments, social rights are of primary importance, because they provide the subject with goods and resources, which make autonomy possible: education, healthcare assistance, welfare, the possibility to participate in the cultural and religious life of one's own community, etc.[7]. Moreover, autonomy requires that the subject is inserted in a relational context suitable for the exercise of freedom, which is characterized by positive relations of recognition: "autonomy is a capacity that exists only in the context of social relations that support it, and only in conjunction with the internal sense of being autonomous"[8]. In other words, autonomous choices, that is choices that can be recognized by the subject as their own and corresponding to their goals[9], depend on a series of support conditions, which are at the same time normative, institutional, and social (or more generically relational). Such a relational theory of autonomy is based "on recognition of the ways in which, as agents, our practical identities and value commitments are constituted in and by our interpersonal relationships and social environment"[10].

Due to this complex interplay between personal capacities, institutional context, and relational resources, autonomy shall be understood as a concept of degree: the social conditions that support autonomy, are at the same time the factors that determine its strengthening or weakening. Personal autonomy depends on a series of attitudes towards oneself and the world – self-esteem, self-respect, and self-confidence – which are, in turn, dependent on relationships of recognition, in both a positive and negative sense. In other words, the relationship that each person has with him/herself is the result of a complex set of social interactions: the normative systems (that recognize the dignity of the person) interact with networks of affective relationships (that shape self-confidence), and with networks of social relationships (that evaluate individual choices and goals)[11]. If this process is positive, subjective autonomy is strengthened and sustained; if the recognition process is negative (because the subject is placed in a context in which his/her choices are despised and devalued, his/her dignity unprotected or misunderstood, or the bonds are a vehicle of humiliation and degradation), subjective autonomy will be severely limited, or otherwise greatly compromised[12].

Journal for the Philosophy of Mind and Action, 6, 2003, pp. 90-108. M. G. BERNARDINI, *Disabilità, giustizia, diritto. Itinerari tra filosofia del diritto e disability studies*, Torino, 2016.

[7] See R. YOUNG, *Autonomy: Beyond Negative and Positive Liberty*, New York, 1986. J. RAZ, *The Morality of Freedom*, Oxford, 1986. M. OSHANA, *Personal Autonomy and Society*, in *The Journal of Social Philosophy*, 29, 1998, pp. 81–102. A. SEN, *Development as Freedom*, New York, 1999.

[8] J. NEDELSKY, *Reconceiving Autonomy: Sources, Thoughts and Possibilities*, in *Yale Journal of Law & Feminism*, 1 (1), 1989, p. 25.

[9] See J. ANDERSON, *Disputing Autonomy. Second-Order Desires and the Dynamics of Ascribing Autonomy*, in *Sats - Nordic Journal of Philosophy*, 9 (1), 2008, pp. 7-26.

[10] C. MACKENZIE, *Relational autonomy, normative authority and perfectionism*, in *The Journal of Social Philosophy*, 39, 2008, p. 519.

[11] See A. HONNETH, *Kampf um Anerkennung. Zur moralishen Grammatik sozialer Konflikte*, Surkamp (tr. by J. Anderson, *The struggle for recognition: The moral grammar of social conflicts*, Cambridge), 1996, p. 173. J. ANDERSON, A. HONNETH, *Autonomy, Vulnerability, Recognition, and Justice*, in J. ANDERSON, J. CHRISTMAN (eds.) *Autonomy and the Challenges of Liberalism. New Essays*, Cambridge, 2005, p. 131.

[12] See *Ivi*, cit., 137.

The relational account of autonomy does not exclude the value of the single individual. On one hand, it is important to protect individual freedom to determine a person's own goals, values, and desires, without being conditioned by the will of other subjects with greater power, more information, or more resources. On the other hand, the relational context, which is supportive toward the subject's choices, and in which these choices are recognised and appreciated, must be taken into consideration. For a subject to make autonomous choices, in short, preventing an external will from overcoming that of the individual is not enough: a supportive context is also necessary. Relationships that bolster self-confidence, self-esteem, and respect are in this perspective just as important as the legal recognition of individual autonomy[13].

3. Relational autonomy and trust

The above-mentioned relevance of the "supportive context" makes the dialectic evident between personal autonomy and trust. Any person may be autonomous (and make autonomous choices) not merely thanks to her inner capacities and resources, but also with regard to certain kinds of relationships, which support both self-trust and trust in other people. If autonomy is not an ideal of independence, referred to people with no ties to others[14], social relationships and trust are causally necessary for it.

A significant amount of literature has been devoted to the analysis of such an interplay. The basic idea is that conditions necessary for the exercise of personal autonomy (e.g. adequate options, information relevant for the decision) depend on the help of others that are trustworthy[15]. In other words, if autonomy is relational, a certain extent of trust in others is essential. What is at stake is, therefore, when and on what conditions trust is justified. More precisely, for trust to be plausible, the parties (both the trustor and the trustee) must have and display attitudes toward one another that permit trust, and they must be trustworthy[16]. By trusting, we acknowledge the fact that we are vulnerable (at least to betrayal), and we express a kind of optimistic aptitude towards others, particularly with regard to their competence in a certain domain. The central existential question we ask when we trust is, therefore, whether it is reasonable for us to trust, given the information we have and the way things appear to us.

If we move towards a typical medical setting, we can translate this question by asking whether, and on what conditions, the patient may trust the health care provider, and may place his/her trust in the complex of health care institutions, including hospital administrators, and the legal and judicial system. In this perspective, to trust in health care providers does not mean waiving the autonomous agency: when we trust we do not waive our goals, our needs, and our values. As Karen Jones writes,

[13] See C. MACKENZIE, W. ROGERS, *Autonomy, vulnerability and capacity: a philosophical appraisal of the Mental Capacity Act*, in *International Journal of Law in Context*, 9 (1), 2013, pp. 42-44.

[14] See V. HELD, *Feminist transformations of moral theory*, in *Philosophy and Phenomenological Research*, 50, 1990, pp. 321–44.

[15] See M. OSHANA, *Trust and Autonomous Agency*, in *Res Philosophica*, 91 (3), 2014, pp. 431–447.

[16] See C. MCLEOD, *Trust*, in E. N. ZALTA (ed.), *The Stanford Encyclopedia of Philosophy*, 2015, https://plato.stanford.edu/archives/fall2015/entries/trust/ (last visited 03/08/2015).

we "hope that what the physician takes to constitute acting with integrity and takes to constitute the interests of her patients will be, at least in part, shaped by the expectations of those patients"[17].

As Joffe and Truog explain, in some medical decisions (those about ends, as well as those about means that necessarily entail choices among ends), physicians function as adviser-fiduciaries to their patients. In other cases, (when considering decisions about means to settled ends) physicians function as agent fiduciaries to their patients[18]. Of course, we are not always guaranteed that a physician will "allow the expectations of her patients to shape her understanding of what, here and now, good medical practice consists in"[19]: for that reason, any autonomous choice of the patient is also in a balance with the trust she must place in the health care and the legal system.

In other words, the fact that personal autonomy is relational (that is, shaped by and exercised in social and relational contexts) means that when we affirm that a person is acting autonomously, we are recognising in her decisions a certain extent of self-governance, of self-authorization, and of self-determination[20], within the interactive dynamic between the people involved. On one hand, these three axes of autonomy are possible because (and to the extent that) the person is participating in social relations that afford her this authority[21]. On the other hand, the person who acts autonomously also: a) expects a benign behaviour from others (doctors, nurses, health care providers, family members, etc.); b) attributes a general integrity on the part of these subjects; c) accepts a certain extent of dependence on these people, as well as the risk and vulnerability connected to this[22]. The person may act autonomously also because her autonomous agency is promoted and reinforced by trust in the other subjects involved, as well as in the complex of relevant institutions and social structures. The deliberative process within which autonomy takes shape is a collaborative partnership: in a medical setting, patients give expression to their expectations and wishes about the care, taking the information received into consideration, and trusting that others will accord to their will a reasonable and respectful consideration[23].

At the same time, to be able to do such an intense epistemic work (is it reasonable for me to trust? Is trust well-grounded? It is justified? How do I evaluate the information I have?) people need, first and foremost, to trust themselves to do it. Analogously, to choose and act according to their values and desires, people need some degree of self-trust: people need to understand themselves as beings whose will and desires will be taken reasonably into account (namely, not underestimated or misrecognised).

Being able to make autonomous choices is a socially constructed attitude, as well as the ability to trust others. In both cases, people need self-trust: they need to be able to understand themselves as trustworthy, people whose decisions, values, and wishes are worthy of consideration. People act au-

[17] K. JONES, "*Trust as an Affective Attitude*" in *Ethics*, 107 (1), 1996, p. 10.

[18] See S. JOFFE, D. TRUOG, *Consent to Medical Care: The Importance of Fiduciary Context*, in F.G. Miller, A. Wertheimer (eds.), *The Ethics of Consent: Theory and Practice,* Oxford, 2010, pp. 353-355.

[19] K. JONES, "*Trust as an Affective Attitude*", cit., p. 10.

[20] See C. MACKENZIE, *Three Dimensions of Autonomy: A Relational Analysis*, in M. PIPER, A. VELTMAN (eds.), *Autonomy, Oppression and Gender*, New York, 2014.

[21] See M. OSHANA, *Trust and Autonomous Agency*, in *Res Philosophica*, 91 (3), 2014, p. 435.

[22] See T. GOVIER, *Self-Trust, Autonomy, and Self-Esteem*, in *Hypatia*, 8 (1), 1993, pp. 99-120.

[23] See M. OSHANA, *Trust and Autonomous Agency*, cit., p. 440.

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tonomously only when they trust in their own ability to be worthy of consideration by others. People's self-conception as marginal, vulnerable, unworthy of consideration, crazy, undermines their sense of self-worth and, hence, their capacity for autonomy. Even if they may be able to reflect and critically understand information, their capacity to form preferences and make decisions are considerably impaired: as Taylor rightly writes, we "define our identity always in dialogue with, sometimes in struggle against, the things our significant others want to see in us"[24]. People's sense of self-worth stems from social and interpersonal networks: self-trust depends, first and foremost, on relationships of recognition, in both a positive and negative sense. Starting from this attitude towards themselves, people build and shape their attitude toward the world: this is the reason why their capacity for autonomous choices, which is their way of interacting with the world, depends on self-trust, self-respect, and self-confidence.

4. Informed consent and trust

The informed consent is the legal instrument that reminds us of the primacy of human autonomy[25]: it allows the individual to make a decision (either to accept or decline healthcare services) freely, without any form of coercion or constraint. More precisely, it is a process (i.e. not a single event), which allows the patient to make an informed and autonomous choice between the healthcare options available, including the option of refusing the service. However, it has not only been criticised for its tacit individualistic conception of personal autonomy – which I mentioned in the first chapter – but also for being at odds with the strengthening of trust within the medical encounter[26]. Or, at least, for being alternative to it[27].

I will briefly discuss to what extent informed consent procedures seem to be alternative to the trust between patient and health care provider; then, I will discuss why such a tension between informed consent and trust is unavoidable, and even necessary. Finally, in a subsequent chapter, I will discuss how to rethink informed consent procedures, in order to make them consistent with the need of interpersonal trust.

In a rightly famous book Neil Manson and Onora O'Neill argue that the current model of informed consent is grounded in a notion of information that is quite abstract and scarcely justified. They highlight that informed consent procedures are a kind of abstract transfer of information between doctors and patients, along standardised lines of conduit. In this perspective, to say that *relevant* and *adequate* information shall be provided to the patient (as any legal instrument actually does) is to assume that information can be classified, and that such a classification is somewhat objective, being for instance dependent on clinical factors or therapeutic protocols[28].

[24] C. Taylor, *The Politics of Recognition*, in C. Taylor, A. Gutmann (eds.), *Multiculturalism: examining the politics of recognition*, Princeton, 1994, p. 33.
[25] See M.D. Kirby, *Informed consent: what does it mean?*, in *Journal of medical ethics*, 9 (2), 1983, pp. 69-75.
[26] See N.C. Manson, O. O'Neill, *Rethinking Informed Consent in Bioethics*, Cambridge, 2007.
[27] See F. Macioce, *Between autonomy and vulnerability: rethinking informed consent in a relational perspective*, 2019 (Forthcoming in *Notizie di Politeia*).
[28] See N.C. Manson, O. O'Neill, *Rethinking Informed Consent in Bioethics*, cit., p. 28.

Additionally, written consent forms containing information that are given to the person, where signature testifies the terms and the limits of the consent, tend to be mere documents detached from the specific features of the interaction between the subject involved. On the contrary, they argue, both informed consent processes, and their ethical value, cannot be properly reduced to legal agreements. Informed consent procedures have to be understood as discursive practices, which take place in webs of social norms and interpersonal transactions: "This rich normative context (…) is occluded or downplayed when we think of communication merely as the transmission or flow of information from person to person"[29].

Human relationships are the framework of autonomous acts and decisions: within these webs of interaction, people express their wishes, make decisions, try to realize their desires and answer to their needs. Thus, the simple fact of exchanging information, which is the premise for these actions, cannot be understood as if it were independent from the action by which the communication is achieved, and from every feature of such a communication. Intentions, behaviours, gestures, and any other act that shape interpersonal communication, are an intrinsic part of the communication itself, rather than being detached (or detachable) from it.

If information is not a pre-existing object of the relationship, we should therefore think of information as something that is produced within a specific relationship, due to the characteristics and purposes of the interaction. For this reason, information is deemed adequate or relevant with regard to what the people involved (in the interaction) do, think, expect, deem as important, as well as to the broader context within which the dialogue takes place. This also means that communication (between doctor and patient, for instance) cannot only fail because of the quantity or the quality of the information provided; it can also fail because of the way this information is elaborated within the context of the discourse, because of the interaction between the parties[30]. Consequently, regardless of the quantity, adequacy, and relevance of the information, the outcome of the communication depends on the relationship and the dialogue between the people involved (doctors, care team, support providers, family members, etc.); this relationship, along with the information received, may indeed bolster interpersonal trust, and guarantee individual autonomy against paternalism and oppression[31].

I am sympathetic to the arguments of Manson and O'Neill, and I am convinced that the precondition of free and informed consent, besides the information received, is the relationship of trust between the parties involved. Moreover, the consistency between their modes of interaction and the necessity to keep mutual trust between them must be guaranteed. In this sense, the information is adequate and relevant *as a function of* the kind of relationship between the parties.

However, as Kukla[32] rightly observed, the focus on ethical aspects of discursive interaction, as well as on the trust between the parties, may be misleading. It may lead to overlooking the fact that the process of obtaining informed consent occurs in settings that are shaped by the asymmetrical rela-

[29] *Ivi*, cit., p. 42.

[30] See B. FRANZ, J.W. MURPHY, *Reconsidering the role of language in medicine*, in *Philosophy, Ethics, and Humanities in Medicine*, 13 (5), 2018, pp. 1-7.

[31] See E. WEIL, *Logique de la Philosophie*, Paris, 1996, p. 24.

[32] See R. KUKLA, *Communicating consent,* in *Hastings Centre Report*, May-June 2009, pp. 45-48.

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tions of authority and power, even when both parties are well intentioned. Once we consider the context where medical encounters take place, we must notice that such a context is unavoidably asymmetrical: "The institutional and material setting of the clinic affords special social and cognitive authority to the doctor. In the context of the clinic, even a patient who has plenty of authority in other social arenas is inherently at the doctor's mercy in various ways"[33].

This is the reason why, as Kukla explains, we talk about patient's *consent*, rather than doctor-patient's agreements, or directives, etc. The term we use displays such a power asymmetry, and the fact that the patient generally accepts one among the different options given by the doctor, or (more frequently) acquiesces to the plan proposed by others. But – more importantly – this is the reason why we need a document with legal force, however formal and rigid it may be. To be more precise, the emphasis we place in the legal force of informed consent, and consequently on the *content* of the written and signed documents that encapsulate consent, is inherent to the discourse interaction, rather than being separable from it. It is not something that blurs the ethical value of the discourse, or that is alternative and separable from it: rather, it is the necessary framework of such discursive interactions. The fact of signing a document with binding force (however bureaucratic it may appear) does change what both the subjects involved are willing to say, to hear, and to understand: the protection that these documents give to them may counterbalance the potential of manipulation, disrespect, coercion, and misplaced trust that is inherent to such an asymmetrical interaction[34]. In other words, even if signing a document is not sufficient to eliminate the asymmetries, these documents enable the parties (and in particular the patient) to re-negotiate their role within the interaction and manage power relations.

Therefore, on one hand, written documents (with their unavoidable traits of formality, rigidity, and generality) do not ensure that communication has occurred rightly, fairly, and properly. Moreover, they do not ensure that the patient has been informed in the right way, and that the consent is veritable, autonomous and consistent with the patient's authentic values and desires. Trust, and trustworthiness, may guarantee the ethical value of consent, by ensuring that the background of understandings and rules about interaction (generally, not made explicit) has been adequately taken into account. In this perspective, Manson and O'Neill are right in saying that "signatures, let alone ticks in boxes, may have legal weight, but they lack ethical weight"[35].

On the other hand, as we have discussed before, legal documents play a pivotal role in medical encounters, given the asymmetrical structure of these interactions. We cannot simply give these documents up, or reduce them to the legal realm, as if they had no ethical relevance and value. On the contrary, they play a pivotal role in counterbalancing and managing power relations between the parties. What is at stake is therefore how to rethink these (formal, legal, and generic) documents, to make them consistent with the need for trust and trustworthiness between the parties, rather than alternative to it.

[33] *Ivi*, p. 47.
[34] *Ibidem.*
[35] See N.C. MANSON, O. O'NEILL, *Rethinking Informed Consent in Bioethics*, cit., p. 192.

5. Rethinking informed consent: some remarks

Consent should be rethought as the outcome of a dialogue, rather than as a provision of a certain amount of information. The decision-making process must primarily guarantee that such information is intelligible and correctly understood by the person; in addition, far from being ethically neutral, the relationship should be based on specific values: it must be reliable, truthful, non-manipulative, not misleading, free from prejudice, oriented to mutual understanding. Moreover, it must be grounded in the recognition of the other person as the partner of a dialogue, that is, as a person whose reasons and needs must always be taken into consideration.

To be more explicit, I argue that informed consent procedures must ensure (and give proof) of an effective dialogue between the parties, with specific consideration of three basic aspects: language, time, and specific vulnerabilities and needs of the person. By giving relevance to these aspects, informed consent procedures can bolster interpersonal trust between the parties, beyond the mere transfer of a certain amount of information. Informed consent documents may be the outcome of a dialogical relationship, only by allowing the parties sufficient time for communication, ensuring a common understanding of the situation, and taking the specific needs of the patient into account.

a) Sharing a common language

First, power asymmetries arise from the use of an overcomplicated or overspecialised language by the healthcare provider. This is the reason why main international instruments concerning informed consent require the use of a plain, lay language, that is a language accessible to the person concerned (for instance, Regulation EU No 536/2014, whereas n. 30: "the potential subject should receive information in a prior interview in a language which is easily understood by him or her"). Health literacy, understood as the capacity of the person to obtain and understand information about health and services, is a key factor that must be taken into consideration. It also encompasses the knowledge of the healthcare system, of its mechanisms, its costs, and its interfaces with secondary care and social services.

By saying that information must be given in a language accessible to the person I do not simply mean that the words used by healthcare providers must belong to the daily language (which may certainly be a wise option). Moreover, to say it by using Habermas' categories, informed consent procedures must rely on the patient's lifeworld, rather than on the system perspective. A common knowledge about the objective world (in medical interactions: knowledge about physical data, tests, examinations, treatments, symptoms, but also life habits, workload, place of residence, etc.), about the social world (the way people relate to others, the social norms they consider binding, values they respect, etc.), and about the subjective world (intentions, thoughts, and wishes; what the patient perceives as good and desirable) must be reached[36]. Long before the provision of the relevant information, it will be necessary that the participants in the interaction define a common horizon for communication, made of cognitive premises and common beliefs within which the communication takes place: oth-

[36] See L. TVEIT WALSETH, E. SCHEI, *Effecting change through dialogue: Habermas' theory of communicative action as a tool in medical lifestyle interventions*, in *Medicine Health Care and Philosophy*, 14(1), 2011, pp. 81-90.

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erwise, however relevant the information may be from an objective point of view, its subjective relevance will be very limited[37].

Therefore, not only a plain language must be used, but evidence must be given that participants in the dialogue addressed each other as equals, and that their values and choices have been met with respect. Evidence must be given that people's point of view and their opinions have been taken into account, explanations have been provided for what is said, and patients have been permitted to ask and raise questions[38], no matter how relevant they might be.

b) Finding adequate time

The second factor that must be taken into account is time: trust and trustworthiness are related to the time available for dialogue and communication. Time constraints are at odds with communicative decision-making, and facilitate strategic action or systematically distorted communication[39]. On the contrary, "trust is generally earned through repeated encounters (…), and it can easily be lost through a perception, even a misinterpreted one, that the other party lacks interest, commitment or skill"[40]. Therefore, adequate time must be given for the medical encounter, and for the informed consent procedure that is an essential part of it.

Allocating adequate time may appear a sort of wishful thinking due to the time constraints resulting from the recurrent cost-cutting policies (in Italy, but not only there); however, I argue that it could be fostered by law. For instance, the Italian legislator seems to be aware of the need for such a requirement: in a provision (which is as unnoticed as it is important) of the new regulation concerning informed consent (art. 1 para. 8 of Italian Act No. 219/2017) it states that "the time of communication between patient and doctor is considered treatment time".

By asking to place this process within a dialogical context, this rule imposes much more than a mere informative burden on professionals. It calls for the specific condition of every person to be taken into account, and to adapt the informative process to the needs of the patient[41]. In other words, the time dedicated to communicate with the patient is the pivotal part of the process of informed consent: patients' needs and their existential situation (values, desires, fears, vulnerabilities, situations of dependency, resources, relational bonds, and any other circumstance that might influence the decision) may become known thanks to it. Moreover, the time devoted to talk to patients, to explain to and motivate them, to listen to their needs and doubts, is as important as the time devoted to therapy or diagnostic workup: that is, it is not a waste of time, but a pivotal part of what doctors and members of care teams are expected to do. The time dedicated to building and consolidating a rela-

[37] See J. HABERMAS, *Faktizitaet und Geltung. Beitraege zur Diskurstheorie des Rechts und des demokratischen Rechtsstaats, Suhrkamp Verlag* (tr. by W. REHG, *Between Facts and Norms. Contributions to a Discourse Theory of Law and Democracy*, Cambridge Mass.), 1996, p. 14.

[38] See L. TVEIT WALSETH, E. SCHEI, *Effecting change through dialogue: Habermas' theory of communicative action as a tool in medical lifestyle interventions*, cit., pp. 81-90.

[39] See T. GREENHALGH, N. ROBB, G. SCAMBLER, *Communicative and strategic action in interpreted consultations in primary health care: a Habermasian perspective*, in *Social science & medicine*, 63(5), 2006, pp. 1170-1187.

[40] *Ivi,* p. 1178.

[41] See M. DI PAOLO, F. GORI, L. PAPI, E. TURILLAZZI, *A review and analysis of new Italian law 219/2017:'provisions for informed consent and advance directives treatment'*, in *BMC medical ethics*, 20(1), 2019, p. 17.

tionship of trust is functional in the decision-making process, and an essential part (even from a legal point of view) of the medical practice[42].

c) Taking vulnerabilities and needs into consideration

The third main feature of informed consent procedures should be the consideration of the specific needs and possible vulnerabilities of the person, in order to tailor the information to the individual. Informed consent documents should therefore provide evidence that these vulnerabilities and needs have been taken seriously into account, and that the information has been given in a way that is appropriate for the person.

Different kinds of vulnerability may become relevant, and different needs should be taken into account. To give some examples, the age of minority, or pregnancy, or breastfeeding, are not in themselves conditions of vulnerability, but they may be in specific situations (e.g. a clinical trial), owing to the specific type of risks and burdens they expose the person to. Similarly, the belonging to a group is not in itself a sufficient reason for being a person considered vulnerable, but it may be the case due to the particular group the person belongs to (a discriminated minority, or people deprived of their liberty)[43]. In a different perspective, being subject to the authority of others, being undervalued by society at large, being deprived of important goods and services, being under sedation, and lacking the necessary linguistic or cultural competences, may be regarded as conditions of vulnerability[44].

Some of these conditions are well known, and expressly mentioned by national and international legal instruments; others are situations of vulnerability that are the outcome of contingent factors, which for instance produce a fear of negative consequences, or other stressful conditions[45]. What is at stake, however, is not to elaborate a definite list of conditions of vulnerability, but to recognise the necessity of tailoring the information to the needs of the person, so as to counterbalance (rather than to increase) the power asymmetries among the parties of the medical encounter.

By asking that healthcare providers provide evidence of the actions they have undertaken, in order to address the specific vulnerabilities of the person who receives the information, I am placing an additional burden on them. They have not only to tailor the information to the specific needs of the person, but they also have to provide evidence of how the informed consent procedure has been tailored (by describing the specific vulnerability they noticed, and the way they have adapted the informed consent in order to take it into account).

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[42] See S. CANESTRARI, *La relazione medico-paziente nel contesto della nuova legge in materia di consenso informato e di disposizioni anticipate di trattamento (commento all'art. 1)*, in *Biolaw Journal – Rivista di Biodiritto*, 1, 2018, p. 24. I. CAVICCHI, *Le disavventure del consenso informato. Riflessioni a margine della legge sul consenso informato e sulle disposizioni anticipate di trattamento*, in *Biolaw Journal – Rivista di Biodiritto*, 1, 2018, p. 100.

[43] See W. ROGERS, *Vulnerability and Bioethics*, in C.A. MACKENZIE, W. ROGERS, S.M. DODDS, *Vulnerability. New Essays in Ethics and Feminist Philosophy*, New York, 2014, p. 64. J. ALDRIDGE, *Working with Vulnerable Groups in Social Research: Dilemmas by Default and Design*, in *Qualitative Research*, 14(1), 2014, pp. 112-130.

[44] See P.J. CANDILIS, *Advances in Informed Consent Research*, in F.G. MILLER, A. WERTHEIMER (eds.), *The Ethics of Consent: Theory and Practice*, Oxford, 2010, p. 337. K. KIPNIS, *Seven vulnerabilities in the paediatric research subject*, in *Theoretical Medicine and Bioethics*, 24(2), 2003, pp. 107–20.

[45] See M. BIROS, *Capacity, Vulnerability, and Informed Consent for Research*, in *The Journal of Law, Medicine & Ethics*, 46, 2018, p. 75.

Such a burden of proof is a way (consistent with the characteristics of legally binding documents) to counterbalance the power asymmetries between the parties involved in a medical encounter. Therefore, it is a feasible strategy to underpin trust (or, at least, to settle the conditions that make the relationship of trust possible): acknowledging the asymmetrical starting point of the relationship between patient and provider, it assumes that the perspective of the subject who is in a position of powerlessness, or of vulnerability, deserves a privileged consideration. The interests, needs, and arguments of the parties are not on a par with each other: and even if a mutual understanding must be the expected outcome for both, providers have additional burdens, which counterbalance (as much as possible) their different starting point and their position within the dialogue.

6. Conclusion

Informed consent procedures are the context within which the subject's autonomy is guaranteed, as well as the outcome of a relationship that fosters interpersonal trust. Rather than being written documents with mere legal value and no ethical value, they could become a powerful instrument to foster interpersonal trust between the parties (for instance, a doctor and a patient, or a researcher and a person enrolled in a trial).

For this purpose, informed consent procedures must be rethought, by taking the relational character of autonomy into consideration. The idea that information can be classified and transferred as a thing must be abandoned: information that is to be given should be tailored to the person who is required to express consent, also considering the specific situation in which such information is to be given.

Moreover, documents certifying informed consent must also guarantee that the entire process is a dialogue, where power asymmetries are (as far as possible) reduced. Furthermore, it must be reliable, truthful, non-manipulative, not misleading, free from prejudice, and oriented to mutual understanding. It must also ensure (and provide evidence) that three basic aspects have been taken into consideration: the language has to be as lay and shared as possible; the time for the dialogue has to be adequate; attention has to be given to the specific vulnerabilities and needs of the person.

By giving relevance to these aspects, informed consent procedures can bolster interpersonal trust between the parties, beyond the mere transfer of a certain amount of information. Informed consent documents may become the outcome (and the proof) of a dialogical relationship, and of interpersonal trust between the parties.

Contents of the Minor's Assent in Medical Research: Differences between the Scientific Literature and the Legal Requirements

*Jaime Fons-Martínez, Fernando Calvo Rigual, Javier Díez-Domingo, Leonardo Nepi, Loredana Persampieri, Cristina Ferrer-Albero**

ABSTRACT: From an ethical and legal point of view, the assent of the minor to participate in a medical study is a subject of great importance. There is still a debate about the requirements to consider this assent valid and binding. This review analyses and compares the contents of the assent from the points of view of the legislation and the scientific literature.

KEYWORDS: Assent; bioethics; clinical research; hard law; informed consent

1. Introduction

Informed consent is one of the fundamental pillars of clinical research ethics, guaranteeing the autonomy of the potential participant in his/her decision to participate or not in an investigation. It consists in a communicative process and a document. The purpose of the informed consent is to protect the autonomy and voluntariness of the potential participant by informing him/her about all the relevant aspects of the study, before enrolment. The consent to participate can be revoked by the participant at any time.

International, European and National legal frameworks recognize both the importance of including children in clinical trials and the need to provide effective and specific protection for this vulnerable group. The best interest of the child is fundamental: this key principle, recognized by the United Na-

* *Jaime Fons-Martínez: Fundació per al Foment de la Investigació Sanitària i Biomèdica de la Comunitat Valenciana (FISABIO). Valencia. E-mail: fons_jai@gva.es; Fernando Calvo Rigual: Servicio de Pediatría Hospital Lluís Alcanyís. Valencia. E-mail: calvo_fer@gva.es; Javier Díez-Domingo: Fundació per al Foment de la Investigació Sanitària i Biomèdica de la Comunitat Valenciana (FISABIO). Valencia. E-mail: jdiezdomingo@gmail.com; Leonardo Nepi: Libera Università Maria Ss. Assunta (LUMSA). Roma. E-mail: nepil@hotmail.it; Loredana Persampieri: Libera Università Maria Ss. Assunta (LUMSA). Roma. E-mail: l.persampieri@lumsa.it; Cristina Ferrer-Albero: Facultad de Enfermería. Universidad Católica Valencia San Vicente Mártir (UCV). Valencia. E-mail: cristina.ferrer@ucv.es. The article was subject to a double-blind peer review process.*

This paper is an extension of the oral communication entitled "Contenidos del asentimiento del menor en investigación médica: diferencias entre la literatura científica y el requisito legal" presented on the V ANCEI Congress, held in Valencia on May 17th and 18th, 2018, and published in their book of papers in Spanish.

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tions Convention on the Rights of the Child of November 20, 1989, has inspired the regulation of clinical trials involving minors at European and national levels.
The informed consent in studies with minors is made up of two parts: the minor's parents or legal guardians[1] have to accept the minor's participation in the study, through the parental informed consent; the child should agree to participate in the study, through the assent (if deemed able to do it). Therefore, the decision-making and legal responsibility of the minor's participation in the study is on the parents, but the minor's opinion is taken into account and, depending on the national legislation, he/she could be required to accept/refuse participation.
The hard law and the scientific literature deal with many aspects of assent, such as its possibility; the conditions to conduct a medical study with minors; the need of the parental consent; aspects about the child's age; the consideration of the minor as mature; his/her capacity to understand the information or the contents that the assent should include and how it should be presented.
This study analyses the contents of the assent with the perspective of the hard law and the scientific literature.

2. Objective

Analyse and compare the contents of the assent from the points of view of the legislation (hard law) and the scientific literature.

3. Material and method

Legal framework

The hard law analysis adopts a systematic approach in the review of measures, taking into account International, European and National laws.
The analysis begins from the Council of Europe's Convention on Human Rights and Biomedicine of 1997 and Additional Protocol concerning Biomedical Research, then continues with the analysis of the European legal framework, both at the EU level and in six countries: Austria, France, Germany, Italy, Spain and United Kingdom.
The search strategy contains documents from 2001. It includes general legal framework of mature minor's role on health care decision-making process; case law on D2001/20/CE or R 1901/2006 or R 536/2014 with regard to the informed consent process/assent of minors; case law with regard to the application of EU legislation in selected countries. Measures of transposition of the Directive were taken and implementing rules of European Regulations where implemented. The aim of the search was to identify and analyse the contents of the Informed consent/Assent by minors.
The databases used are Eurlex for the European Law and transposition measures in National regulation[2]; IURE for the European case Law; n-Lex for the national regulation on assent; Iurifast and Dec

[1] To facilitate the reading of the text, we will refer to the parents only from this moment, but it also includes the legal guardians of the minor.
[2] Search as described in http://eur-lex.europa.eu/collection/nlaw/mne.html?locale=en (CELEX number search).

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Nat for the member State case law which deal with the application of EU law; and the Common Portal of Case Law[3] for the national case law.
The search, screen and decision of including or not a result of finding has been done by pairs of reviewers by members of the LUMSA research unit involved in the i-CONSENT project.

Scientific Literature

Systematic search with PubMed[4] of experimental, observational and theoretical articles (case reports were excluded); published in English or Spanish; during the last 10 years; that include aspects about the information that is given or should be provided to the minor during the assent process in research.
Review of articles resulting from the search was done by pairs (by title and abstract), discrepancies were resolved by a third person. A critical reading and summary of the selected articles was made, with assignation of quality of the article, using the Osteba's Critical Appraisal Tools[5]. The review of the scientific literature was done by members of the FISABIO and UCV research units involved in the i-CONSENT project. The search in Pubmed was done on the 10th of July of 2017.

4. Results and discussion

Legal framework:

International and European legislation

The Convention on Human Rights and Biomedicine of 1997 (Oviedo Convention)[6] in its article 6, highlights the importance of the assent of the minor to any intervention in the health field, indicating that even the authorization should be given by the representative of the minor or an authority or a person or body provided for by law, the opinion of the minor will be taken into account, in proportion to his age and maturity. The EU Charter of Fundamental Rights[7] also expresses the importance of letting minors express themselves freely and taking their opinion into account in accordance with his/her age and maturity.
Regulation (EU) 536/2014[8] indicates the minimum contents of informed consent for clinical trials (article 29, section 2), and the requirements to obtain consent. According to it, informed consent must include: the nature, objectives, benefits, implications, risks and inconveniences of the clinical trial;

[3] http://network-presidents.eu/rpcsjue/ using Eurovoc Thesaurus (Edition 4.3)
[4]The search strategy used in Pubmed was: ((("Informed consent"[Mesh] OR "assent"[All Fields]) AND "Ethics"[Mesh] AND ("Research"[Mesh] OR "clinical research"[All Fields])) OR (("Informed Consent By Minors"[TW] OR "Consent Forms"[TW] OR "assent"[All Fields]) AND ("Ethical Theory"[TW] OR "Principle-Based Ethics"[TW] OR "Ethics,Research"[TW] OR "Research"[TW] OR "Clinical research"[All Fields]))) AND (English[lang] OR Spanish[lang]) AND ("infant"[TW] OR "child"[TW] OR "adolescent"[TW] OR "minors"[TW]) AND ("2007/07/14"[PDat]: "2017/07/10"[PDat]).
[5] http://www.lecturacritica.com (last visited 9 April 2019).
[6] ETS No.164, *Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine*, 1997.
[7] *Charter of Fundamental Rights of European Union*, 2000 (2000/C 364/01).
[8] 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.

the subject's rights and guarantees regarding their protection, in particular his/her right to refuse to participate and the right to withdraw from the clinical trial at any time without any resulting detriment and without having to provide any justification; the conditions under which the clinical trial is to be conducted, including the expected duration of the subject's participation in the clinical trial; the possible treatment alternatives, including follow-up measures, if the participation of the subject in the clinical trial is discontinued. The information must be comprehensive, concise, clear, relevant, and understandable to any person, provided in a prior interview with a member of the investigating team who is appropriately qualified according to the law of the Member State concerned. The article also indicates that the information should be provided in an interview with a member of the investigation team. During the interview, special attention must be paid to the information needs of specific patient populations and of individual subjects, as well as to the methods used to give the information. The article 2 of Regulation defines the minor as a "subject who is, according to the law of the Member State concerned, under the age of legal competence to give informed consent".

Article 32 of that Regulation specifies that the legal guardian of the minor is the one who should authorise the participation of the minor, but also indicates that the minor must receive the information described in Article 29, adapted to his/her age and mental maturity, by researchers or members of the research team with training or experience in dealing with minors. Specific contents are not specified for assent in minors, considered the same as for informed consent. This article also indicates that the minor's involvement in the informed consent procedure shall be adapted to his/her age and mental maturity.

Article 93 of Regulation (EU) 536/2014[9], establishes the right to confidentiality in clinical trials. Regulation (EU) 2016/679[10], in its 8th article stipulates that the minor should be at least 16 years to give the consent to the processing of his or her personal data (national laws may provide a lower age, but not below 13 years old). If he/she is younger than the stipulated age, the authorization will be granted by the minor's legal guardians.

The informed consent is also necessary when biological samples or health data are collected and stored. Biobanking is an important issue to consider in relation to clinical trials. Privacy and data protection in biobanking is essential for securing acceptance of biobank research across Europe. The Article 22 of Council of Europe Convention on Human Rights and Biomedicine of 1997 establishes that "When in the course of an intervention any part of a human body is removed, it may be stored and used for a purpose other than that for which it was removed, only if this is done in conformity with appropriate information and consent procedures". The European Union's existing regulatory framework in biomedical research, does not have a specific regulation for biobanks. Biobanks are governed under the general regulatory framework for biomedical research. Likewise, the Directive

[9] REGUL ATION (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, cit.

[10] REGULATION (EU) 2016/679 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).

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2004/23/EC[11] on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissue and cells, does not cover research using human tissue (Recital 11 and Article 1).

National legislation

The analysis of the national legislation shows that not all States considered have already implemented Regulation (EU) 536/20142 and that the age at which the minor is considered mature enough to understand the information and to consent to participate in a clinical trial varies, being a regulated aspect only at the national level (see table 1).

Table 1. Aspects about the age criteria; assent and dissent by country

	AGE CRITERIA	MINORS YOUNGER	MINORS OLDER	ASSENT	DISSENT	NATIONAL LEGISLATION
UNITED KINGDOM	16	Consent must be provided by parents or legal representative	They are considered as competent adults for decisions on clinical trial participation	Not expressly required	The explicit wish of a minor capable to form an opinion is considered by the researcher	Medicine for Human Use Regulation of 2004[12]
ITALY	18	Consent must be provided by parents or legal representative	The consent of the child may be considered if, on a case-by-case basis, the maturity of the child is established	Not expressly required	The explicit wish of a minor capable to form an opinion is considered by the researcher	D.lgs. 211/2003[13]
SPAIN	12	Consent must be provided by parents or	Children must give their consent in addition to the	Required for minor over 12 years old	The researcher must respect the minor's dissent	Royal Decree 1090/2015[14]

[11] DIRECTIVE 2004/23/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

[12] The Medicine for Human Use (Clinical Trials) Regulation n. 1031/2004.

[13] Decreto Legislativo 24 giugno 2003, n. 211. Attuazione della direttiva 2001/20/CE relativa all'applicazione della buona pratica clinica nell'esecuzione delle sperimentazioni cliniche di medicinali per uso clinico.

[14] Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de tica de la Investigación con medicamentos y el Registro Español de Estudios Clínicos.

		legal representative	consent provided by parents or legal representative			
GERMANY	18	Consent must be provided by parents or legal representative	The consent of the child may be considered if, on a case-by-case basis, the maturity of the child is established	Required if the minor can understand the nature and implication of clinical trial (case by case approach)	The researcher must respect the minor's dissent if the minor can comprehend the nature and the implications of clinical trial (case by case approach)	Medicinal Product Act 2005[15]
FRANCE	18 or 16 in the case of emancipated minor, not living with parents and eventually having his/her own family	Consent must be provided by parents or legal representative	Emancipated minor is considered as a competent adult in decisions on clinical trial participation.	Not expressly required	The dissent of the child considered sufficiently mature must be taken into account	Public Health Code of 1953 (amended in 2004,2009 and 2016)[16]
AUSTRIA	18	Consent must be provided by parents or legal representative	The consent of the child must be considered in addition to the consent provided by parents or legal representative if he or she is 14 years old and sufficiently mature	Required if the minor is 14 years old and sufficient mature	The dissent of the child considered sufficiently mature must be taken into account	Austrian Medicinal Product Act 185/1983 (emended in 2004)[17]

Source: Compilation by the authors based on the above-mentioned legislation.

[15] Gesetz ber den Verkehr mit Arzneimitteln (Arzneimittelgesetz - AMG) 2005.
[16] Code de la Santé Publique.
[17] Bundesgesetz vom 2. März 1983 über die Herstellung und das Inverkehrbringen von Arzneimitteln (Arzneimittelgesetz – AMG).

Regarding the information provided to the minor or his/her legal representative, there is a broad uniformity (table 2), but neither the European legal framework nor the national standards considered take into account the literacy of the minor or his/her family.

Table 2. Information provided to the minor before the beginning of the clinical trial by country

Country	Information provided to the minor
UNITED KINGDOM	According to Medicine for Human Use Clinical Trials Regulations of 2004, the child must receive information according to their capacity of understanding from staff with experience with minors regarding the trial, its risks and its benefits. Paragraph 3 (1) of Part 1 of Schedule 1 establishes in a general way that the person involved in the research must have met with the researcher and been informed of the objectives, risk and inconveniences of the trial and the conditions under which it is to be conducted. The participant must also be aware that they will be involved in the research before starting the treatment. Further information on the content of the information is provided by the BMA guidelines, which are taken into account by the judge in any consequent judgment.
ITALY	Article 4 of Legislative Decree 211/2003 establishes that children must be informed by staff experienced in dealing with minors about the clinical trial, risks and benefits, in an appropriate manner to their capacity of understanding.
SPAIN	According to article 4 of Royal Decree 1090/2015, in the case of patients with special vulnerabilities, including minors, the person participating at the trial shall be informed about the access to the normal clinical practice for his/her pathology. Article 5 indicates that all clinical trial with minors must comply, in addition to the conditions established in Articles 3 and 4 of the Royal Decree, all those listed in Article 32 of Regulation (EU) No. 536/2014 of the European Parliament and the Council.
GERMANY	Chapter 6, Section 40 (4) of the Medicinal Product Act of 2005 indicates that "before the start of the clinical trial, the minor shall be informed, by an investigator who is experienced in dealing with minors who is a doctor or, in the case of a dental trial, a dentist or an adequately experienced member of the investigating team who is a doctor or, in the case of a dental trial, a dentist, about the trial, the risks and benefits, in so far as this is possible, taking into account the minor's age and mental maturity".
FRANCE	Article L- 1122-2 of the Public Health Code of 1953 indicates that non-emancipated minors that will participate in a research, should get infor-

	mation provided in Article L. 1122-1 adapted to their ability to understand. The article L. 1122-1 indicates that the information has to include: the objective, methodology and duration of research; the expected benefits and foreseeable risks, even if the trial ends earlier than expected; possible medical alternatives; the medical care provided at the end of the trial if such assistance is required; the opinion of the committee referred to in Article L- 1123-1 and the authorization of the competent authority referred to in Article L-1123-12; if necessary, prohibition of simultaneously participating in another search; information about how personal data will be handled; information about the right to receive health data held by the investigator; information about the right to refuse to participate in research or to withdraw consent without incurring any harm.
AUSTRIA	According to §42 of Austrian Medicinal Product Act 185/1983, prior to commencing the clinical trial, the minor must receive and understand appropriate information about the nature, significance, scope and risks of the clinical trial. The minor always has to be informed by an investigator who is experienced in dealing with minors, who must take into account the stage of maturity of the child.

Source: Compilation by the authors based on the above-mentioned legislation.

About confidentiality and privacy, domestic laws do not provide specific norms on the condition of minors who exercise these rights through their legal representatives. Following the analysis of applicable European legislation, it is clear that even in the field of scientific research, the specific consent of the person is necessary for the use of their personal data. In the case of clinical trials involving minors, the ability to provide informed consent must be examined also for consent to the handling of data.

It has been observed that, in spite of the fact that, in many aspects, there is uniformity between the different national legislations and with respect to European legislation, in others, there are still discrepancies. Some of these differences are in relevant issues such as the child's participation in the decision-making process.

What does the scientific literature tell us?

The scientific literature presents the assent as a process that respects and promotes autonomy in the child's development, to express his/her opinion and decide on the health or illness processes that affect him/her. The empowerment and the development of their moral capacity for the autonomous exercise of future decisions are pursued[18,19].

[18] B.J. Pinto Bustamante, R. Gulfo Díaz, *Asentimiento y consentimiento informado en pediatría: aspectos bioéticos y jurídicos en el contexto colombiano*, in *Revista Colombiana de Bioética Universidad El Bosque*, 8(1), 2013, p. 154.

[19] Y. Unguru, *Making sense of adolescent decision-making: challenge and reality,* in *Adolescent medicine: state of the art reviews,* 22(2), 2011, p. 198.

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Although much has been written about assent, there is still no agreement in several aspects about this topic, such as the quantity and quality of the information that must be provided to the child or the information that they really want and need to know, among others.
In the literature review carried out, 306 results were obtained from the search strategy, but only 10 articles (1 experimental, 6 observational and 3 theoretical) analysed aspects about the information that is provided or should be provided to the minor during the process of informed consent or assent. Of these, 3 were considered to have high quality by the reviewers, 2 medium quality, 4 low quality and 1 was not classifiable due to the lack of data after critical reading, as shown in table 3.

Table 3: Studies on the information of the assent, according to the quality of the evidence

First Author, Year	Quality of evidence[20]	Type of study	Nº subjects
Unguru, 2010[21]	High	Observational study	37 interviews with children (7 – 19 years)
Tait, 2018[22]	High	Experimental study	55 minors/55 parents (minors: 8-12 years; 13-17 years)
Lee, 2013[23]	High	Observational study	123 minors (12 - 17 years)
Dove, 2013[24]	Medium	Observational study	43 paediatric consent forms
Tait, 2017[25]	Medium	Observational study	20 expert stakeholders
Roth-Cline, 2013[26]	Low	Theoretical study	Not applicable
Twycross, 2008[27]	Low	Theoretical study	Not applicable

[20] Considered by the reviewers using Osteba's Critical Appraisal Tools.
[21] Y. Unguru, A.M. Sill, N. Kamani, *The experiences of children enrolled in pediatric oncology research: implications for assent,* in *Pediatrics*. 125(4), 2010, pp. 876-883.
[22] A.R. Tait, M.E. Geisser, L. Ray, R.J. Hutchinson, T. Voepel-Lewis, *Disclosing Study Information to Children and Adolescents: Is What They Want, What Their Parents Think They Want?,* in *Academic pediatrics*, 18(4), 2017, pp. 370-375.
[23] S. Lee, B.G. Kapogiannis, P.M. Flynn, B.J. Rudy, J. Bethel, S. Ahmad et al., *Comprehension of a simplified assent form in a vaccine trial for adolescents*, in *J Med Ethics*, 39(6), 2013, pp. 410-412.
[24] E.S. Dove, D. Avard, L. Black, B.M. Knoppers, *Emerging issues in paediatric health research consent forms in Canada: working towards best practices*, in *BMC Medical Ethics*, 14(5), 2013, pp. 1-10.
[25] A.R. Tait, M.E. Geisser, *Development of a consensus operational definition of child assent for research*, in *BMC Medical Ethics,* 18(41), 2017, pp. 1-8.
[26] M. Roth-Cline, R.M. Nelson, *Parental permission and child assent in research on children,* in *The Yale journal of biology and medicine,* 86(3), 2013, pp. 291-301.
[27] A. Twycross, F. Gibson, J. Coad. *Guidance on seeking agreement to participate in research from young children*, in *Paediatric nursing*, 20(6), 2008, pp. 14-18.

Baker, 2013[28]	Low	Observational study	20 minors/ 57 parents
John, 2008[29]	Low	Observational study	73 children (6-8 years old)
Giesbertz, 2016[30]	Not classifiable	Theoretical study	Not applicable

Source: self-made

Tait and Geisser[31] did a Delphi study with a panel of expert stakeholders to provide consensus about the definition of child assent for research study. They highlight the importance of providing information appropriate to the child's age, taking into account their cognitive and emotional aspects, such as it can be read in the final definition of assent proposed in the study:

"Children who lack the legal authority to provide informed consent per state laws should provide their assent to participate in a research study unless they either lack the cognitive ability, their clinical condition precludes their ability to communicate a choice, or the research holds out the prospect of direct benefit that is only available in the context of the research. Assent is an interactive process between a researcher and child participant involving disclosure of cognitively and emotionally appropriate information regarding, at minimum, why the child is being asked to participate, a description of the procedures and how the child might experience them, and an understanding that participation in the study is voluntary. Children should understand that they can decline participation or withdraw from the study at any time. Assent requires that the child explicitly affirms his or her agreement to participate in a manner that reflects their age-appropriate understanding and that is free of undue influence or coercion. In the absence of an explicit agreement, mere failure of the child to object cannot be construed as assent"[32].

Analysing the information that the assent should include, they consider essential to inform about the reasons why he/she has been chosen to participate; the procedures and how he/she will experience them; the indirect benefits if there is no expectation of personal benefit; and about the voluntariness and the right to revoke at any time. Understanding this basic information is paramount and the child should be aware of how it will affect his/her personal situation. The freedom of the child to decide about his/her participation in the study without any undue influence or coercion was also pointed out. It is interesting to highlight that during the Delphi process the experts suggested to change "must provide assent" with "should provide assent", making it a recommendation more than an obligation.

[28] J.N. Baker, A.C. Leek, H.S. Salas, D. Drotar, R. Noll, S.R. Rheingold, et Al., *Suggestions From Adolescents, Young Adults, and Parents for Improving Informed Consent in Phase 1 Pediatric Oncology Trials,* in *Cancer*, 119(23), 2013, pp. 4154-4161.

[29] T. John, T. Hope, J. Savulescu, A. Stein, A.J. Pollard, *Children's consent and paediatric research: is it appropriate for healthy children to be the decision-makers in clinical research?*, in *Archives of disease in childhood*, 93(5), 2008, pp. 379-383.

[30] N.A. Giesbertz, K. Melham, J. Kaye, J.J. Van Delden, A.L. Bredenoord, *Personalized assent for pediatric biobanks*, in *BMC Medical Ethics*, 17(59), 2016, pp. 1-7.

[31] A.R. Tait, M.E. Geisser. *Development of a consensus operational definition of child assent for research*, cit., p. 1-8.

[32] A.R. Tait, M.E. Geisser. *Development of a consensus operational definition of child assent for research*, cit., p. 4.

Previously, Roth-Cline and Nelson[33] had already sought evidence regarding the information that the assent must contain. In their review of the literature, they found that there is considerable disagreement about important aspects of the assent, such as: "the age at which investigators should solicit assent from children; how to resolve disputes between children and their parents; who should be involved in the assent process; the relationship between assent and consent; the quantity and quality of information to disclose to children and their families; how much and what information children desire and need; the necessity and methods for assessing both children's understanding of disclosed information and of the assent process itself; and what constitutes an effective, practical, and realistically applicable decision-making model"[34].

They noted that the regulations do not specify the information necessary for the assent, but identify factors to take into account when assessing the minors' capacity, such as the age, maturity and psychological state.

They point out that the minor should understand at least why he/she has been asked to participate and the procedures to be carried out, and must agree to participate, whether parents are provided with more detailed information (such as risks, benefits or alternatives), reinforcing the importance of parental permission during the process. They concluded that the amount of information a child should understand should vary with his/her age and maturity, and argue that the model of assent in adolescents should be different from that of younger children; even so, they cannot affirm with scientific evidence the sections of information that must be included in each assent.

Including the same contents in the informed consent and the assent, as stipulated in the regulation, can also be criticized if we take into account the words of Unguru: when he talks about consent for clinical treatment, he notes that informed consent and assent are not the same and that they are based on different terms, informed consent is based on competence, while assent is based on capacity[35]. This difference may also be valid for clinical research where assent or consent requires a more nuanced and refined decisional capacity than in clinical treatment[36].

But one thing is what the legislation, experts in pediatric bioethics and researchers decide, and another one is the information that children consider relevant for themselves. A study conducted by Tait et al.[37] with 55 parent-child dyads compares the information priorities on research among adolescents (13-17 years) and younger children (8-12) and what the parents consider important to their child. They conclude that for minors and parents (what they believe is important for their children) all the contents are important, but they differ in some aspects. The main interests for the children focus on the procedures of the study, confidentiality and the direct and indirect benefits. There are statistically significant differences in the interests depending on the age of the minor. Adolescents prioritise more the information about voluntarism, direct benefits and procedures, than the younger minors. Comparing the importance given by minors to the information and parent's perceptions of what is relevant for their children statistically significant differences are found in the greater im-

[33] M. Roth-Cline, R.M. Nelson. *Parental permission and child assent in research on children,* cit., pp. 291-301.
[34] M. Roth-Cline, R.M. Nelson. *Parental permission and child assent in research on children,* cit., p. 296.
[35] Y. Unguru, *Making sense of adolescent decision-making: challenge and reality,* cit., p. 198.
[36] Y. Unguru, *Making sense of adolescent decision-making: challenge and reality,* cit., p. 200.
[37] A.R. Tait, M.E. Geisser, L. Ray, R.J. Hutchinson, T. Voepel-Lewis, *Disclosing Study Information to Children and Adolescents: Is What They Want, What Their Parents Think They Want?*, cit., pp. 370-375.

portance that children attach to confidentiality and the lesser importance given to the purpose of the study and the direct benefits.

Parent's perceptions about the child's information priorities also vary depending on the age and gender of the child. They consider that girls will be in general more interested in all the information than boys, except in the case of the information about alternatives that parents consider less important for girls under 13 years than for boys of the same age group. Other statistically significant differences by gender are the priorities of information about the procedures (higher in girls than boys in both age groups) and about the purpose of the study, the direct benefits, the voluntarism and the right to withdraw in any moment (higher in adolescent girls). There are also statistically significant differences in parents' perceptions depending on the child's age, considering that adolescent girls give more importance to information about the purpose of the study and the alternatives than younger girls; and that adolescent boys care more about risks and confidentiality than younger boys. The study also shows that children and adolescents make decisions with parents and investigators, and that they perceive a beneficial effect of shared decision-making.

Unguru, Sill and Kamani[38] also studied the children's preferences about information related to research. They found that most children consider important to know why research is done before being asked to enrol in it, and some consider that it would be useful to be able to talk to other children with experience participating in research to help them understand what participation in a study entails. Another important factor that appears in this study is that some minors enrol or remain in studies because they feel pressured by their parents or physicians. More than one third of the children did not feel free to dissent and half of the children believed that they had little, very little or no role in deciding to enrol or not in the study. By asking minors how they can be more involved, they point out several things that the physician can do, such as talking directly to them and not only to their parents; ask them about their concerns; speak in an understandable language for them or do not treat them as children just because of their age.

As for the involvement of the children in the decision-making, in a study conducted by John et al.[39], in 2008, with young healthy children (6-8 years) who had participated in a study on a vaccine, most parents and several children considered that the parents should be the ones making the decision about the children's participation in the study. It was concluded that the majority of children between 6-8 years do not have the ability to understand the factors surrounding a clinical study, with marked individual differences. They highlighted that these important individual differences in understanding among children of this range of age, makes inappropriate to provide them with all the information about the study, and consider very important the role of the parents directing how capable the child is to understand this information and guiding the meeting of the child with the healthcare professionals. The authors indicate that these results cannot be extrapolated for older children.

[38] Y. Unguru, AM. Sill, N. Kamani, *The experiences of children enrolled in pediatric oncology research: implications for assent*, cit., pp. 876-883.

[39] T. John, T. Hope, J. Savulescu, A. Stein, A.J. Pollard, *Children's consent and paediatric research: is it appropriate for healthy children to be the decision-makers in clinical research?*, cit., pp. 379-383.

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Regarding the amount of information, Baker[40] in a qualitative study using coded interviews carried out in 2013, tried to identify how to improve the quality of the Informed Consent Process received from parents and adolescent and young adult patients (aged 14-21 years) in a Phase I pediatric oncology trial. From the interviews carried out with 20 children between 14 - 21 years old and 57 parents, it was extracted that the most frequent suggestions were related to the information given during the assent process. More information was demanded about the risks, benefits, purpose of the study, scientific grounds that justify their participation and objectives and logistical issues specific to Phase I trials. The respondents expressed their willingness to have a process based on honest communication, without technicalities, adapted to the needs of children and their families. They also suggested that the written information included in the informed consent could be sent in advance, that other formats be used in addition to the written one and that they be provided with a summary sheet with the key aspects, which should be kept in mind during the study development. They also appreciate having more time to make the decision; that the physician explains the study several times, ensures their understanding, has a follow-up meeting to allow the family to discuss their options and guides them in the decision about participating.

This personalization of the agreement tailored to the needs of the child has also been proposed by Giesbertz et al.[41] in a theoretical study in which they tried to answer the question about how the content and the process of assent should be personalized to the child in the specific case of biobanks. Although the lack of data of this publication makes its quality unclassifiable, the article states that for the information to be personalized, it must begin with concrete information (that is easier to understand) and continue providing more information at the child's request, according to his/her desires and capacities. It is recommended not to use only the classic written format, but also different techniques and technical innovations and styles. Information technologies can play an important role to facilitate continuous communication.

In an analysis of the thematic content of paediatric informed consent models by Dove et al.[42], performed with Canadian consent forms, they observed a lot of variability between consent forms and that many of them presented important information gaps. For example, some consent forms did not include aspects such as the child's ability to dissent, the possibility to withdraw, details about the transfer and data sharing or the scope of parental right to access information concerning their child. The majority did not consider cumulative or non-physical risks. Some forms presented a lack of specificity about the role of the minor in the decision-making or the procedures to resolve conflicts in the decision-making between parents and minors.

Looking into the importance of understanding, Lee et al.[43] evaluated in 2013 the comprehension of a modified document in text format with supporting images for a clinical trial of Hepatitis B vaccine.

[40] J.N. Baker, A.C. Leek, H.S. Salas, D. Drotar, R. Noll, S.R. Rheingold, et al., *Suggestions From Adolescents, Young Adults, and Parents for Improving Informed Consent in Phase 1 Pediatric Oncology Trials,* cit., pp. 4154-4161.

[41] N.A. Giesbertz, K. Melham, J. Kaye, J.J. Van Delden, A.L. Bredenoord. *Personalized assent for pediatric biobanks*, cit., pp. 1-7.

[42] E.S. Dove, D. Avard, L. Black, B.M. Knoppers. *Emerging issues in paediatric health research consent forms in Canada: working towards best practices*, cit., pp. 1-10.

[43] S. Lee, B.G. Kapogiannis, P.M. Flynn, B.J. Rudy, J. Bethel, S. Ahmad, et al. *Comprehension of a simplified assent form in a vaccine trial for adolescents*, cit., pp. 410-412.

They found that only 56% of the children answered correctly all the questions (six). The issues better understood in the assent were those related to randomization and the possibility of withdrawing from the study; the worst-understood issue was the blinding of the choice of vaccine. They suggested that the inclusion of a quiz in the process of assent could have a positive impact to assess the understanding of the information and ensure the complete comprehension of the study.

Twycross, Gibson and Coad[44] tried to establish a formula so that the information provided to the minors involved in research is appropriate. Through meetings with experts conducted during the Research Society's International Nursing Research Conference, a consensus was reached regarding the information that needs to be provided to the minor and the format that the information should have. The National Research Ethics Services (NRES) consider that the following information needs to be provided[45]:

- "What is meant by research (or a project).
- That they are being invited to take part in research.
- Who else will be taking part (and how many).
- That agreement to take part in the study is voluntary (even if their parent/carer has agreed). They can still say no at any time.
- What the research is about.
- What the researcher will do.
- What they have to do.
- How long it will take.
- Any benefits or anything good that will come from the research; if there are none, say so.
- If there is a reward then you should say.
- That the information they provide is private, unless the child discloses that he or she or someone else is at risk of harm.
- A contact person for further information."

The recommendations about the format are[46]:

- "The information should be kept to a manageable length, in keeping with age and development.
- The sheet should be no more than one double-sided A4 page (excessively detailed information sheets can overwhelm participants).
- The leaflets should be designed so that they can be read to the child but are interactive enough for them to engage in the process.
- The language used needs to be appropriate to the age and developmental stage of the child.
- Pictures can be used to increase engagement but ensure they are appropriate to the child's development, prior learning and setting.

[44] A. Twycross, F. Gibson, J. Coad. *Guidance on seeking agreement to participate in research from young children*, cit., pp. 14-18.
[45] A. Twycross, F. Gibson, J. Coad, *Guidance on seeking agreement to participate in research from young children*, cit., p. 18.
[46] A. Twycross, F. Gibson, J. Coad, *Guidance on seeking agreement to participate in research from young children*, cit., p. 16.

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- Do not just increase the size of the typeface of an information leaflet originally designed for older children.
- Information leaflets should be printed on the headed paper of the hospital/ institution where the research is being carried out. Plain paper is not acceptable even for young children.
- Information leaflets need to include the information required for informed consent, as set out by NRES. This might mean being creative in the way you phrase the question or provide the information or else the young child might not fully understand."

Many of these recommendations allude to aspects of legibility, both linguistic (grammatical and lexical) and typographic (graphic characters), which will allow the child to read and understand it more easily.

In the same study, Twycross et al. explored other interesting aspects such as the age at which minors can give a "so-called informed agreement" to participate in a research study or how to verify that the minor has understood the information. Concerning the age, they indicated that if the information is presented in an appropriate way, children from 18 months or 2 years old could already give informed agreement to participate in the study. They recommended to verify the understanding of the minor by asking him/her to repeat back to the researcher what the project is about and what their participation will involve, or include a written or picture-based list of questions to be answered at the end of the information sheet.

5. Conclusion

Even if the importance of minors' participation in clinical research is highlighted in the legal and scientific documents, there is a lack of high quality studies conducted in Europe on this topic that make it difficult to draw conclusions. The topic of the contents of the assent has not been explored at depth, probably because the legal texts establish the contents and they are the same as for the informed consent in adults. The focus has been usually put on the adaptation of the content to the age and maturity of the minor, the understanding of the document, the profile of the person who should give this information and the importance devoted to the minor's opinion.

Analysing the European legal framework, the specific issue of informed consent in the context of clinical trials involving minors allows us to identify some key points: a) the rule takes into account the proxy consent that must be provided by parents or other legal representatives; b) Regulation No. 536/2014 (Article 32, Clinical trials on minors) requires the child to receive the information referred to in Article 29(2) in a manner appropriate to their capacity of understanding, provided by staff with experience with minors; c) the explicit dissent to start or continue research participation at any time expressed by a minor who is capable of forming an opinion and assessing the information relevant to participation in the clinical trial must be considered by the investigator.

Comparing the legislation with the scientific literature, it has been seen that there are differences in the information that the assent should include from the point of view of the legislators, researchers, parents, and minors (being also different the priorities for adolescents and younger children). There is also a current debate about the convenience of giving the minor all the information (adapted to his/her age and maturity) or giving only some contents to them (also according to his/her age and

maturity and taking into account that all the information is given to parents in their consent). Even so, there are some contents that are identified most of the times as essential in the assent, such as why they have been asked to participate, the study procedures, the voluntariness of participation or the option to leave the study at any time. There is no agreement on the age at which the child's opinion should be taken into account, nor about the role that parents should play during the information phase and the child's decision-making process.

There are differences about the information that the investigators and the parents consider relevant for the minors and that the minors consider relevant for themselves. This should be taken into account when investigators or parents inform minors, as probably they will give the information that they consider relevant to minors and not what minors consider relevant for themselves. The information that the parents deem important for minors is different according to gender and age, so the impact of gender on the information process should also be taken into account when parents inform minors or help them during the decision-making process.

More studies about the interests and needs of the minors are needed to adapt better the contents and the process of assent to them instead of considering that adults and minor have the same needs of information.

In addition to what is said (content and quantity), it is relevant how it is said (method/format used, information order, legibility), who says it (skills of the person reporting), how many times it says it (continuity and adaptation of the information throughout the study) and what the child wants to know or cares about.

It is also essential to ensure an adequate understanding of the information. Additional actions such as personalising the process, talking directly to minors and soliciting their concerns, asking minors to repeat back the information provided, including a quiz in the process of assent or giving him/her the possibility of talking with other minors with previous experience participating in clinical trials may have a positive impact in the process and contribute to ensuring the comprehension of the information and involving minors in the decision-making.

The role of the minor in the decision-making also needs to be better set. The legal documents give importance to the minor's opinion through the assent (depending on their age and maturity), but the scientific literature suggests their lack of influence in the decision-making. Moreover, the scientific literature shows the lack of efforts or mechanisms to ensure that the opinion/wish of the minor to participate in research is taken into account, neither to facilitate the understanding of the information by the minor and their parents. Legal documents have a key role in the consideration and importance given to both aspects, in setting out standards and requirements.

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Ethical Issues Concerning the Informed Consent Process in Paediatric Clinical Trials: European Guidelines and Recommendations on Minor's Assent and Parental Permission

Leonardo Nepi*

ABSTRACT: Appreciation for minors' involvement in clinical trials and for children's autonomy is growing, but has to be combined with the parental and social duty to protect them. In recent years the ethical debate had shifted to specifically encouraging children's inclusion in trials, taking into account the benefit they can obtain, both direct and indirect. Nevertheless, there is a risk concerning the protection of children's rights and the proper acquisition of informed consent could become a legal and ethical issue. The article examines the ethical framework concerning informed consent in paediatric clinical trials at European level, with special reference to guidelines, recommendations and opinions issued by national, European and international bioethics/research ethics committees, scientific societies, European institutions and international organizations. The review aims at pointing out key issues regulated by common ethical standards and grey areas in which soft law regulation is still evolving. The focus is devoted to the topics of assent, parental permission and shared decision-making, analysed in the light of the general principle of child's best interest.

KEYWORDS: Informed consent; paediatric clinical trials; assent; parental permission; child's best interest

SUMMARY: 1. Introduction – 2. The inclusion of minors in clinical trials – 3. The balance between risks, burdens and benefits (direct and indirect) – 4. The role of parents – 5. Children and mature minors: different age, different issues – 6. Assent and parental permission – 7. Objection from the child – 8. Shared decision-making: from a legal point of view to an ethical perspective.

1. Introduction

Informed consent, parental permission and assent are both parts of a communication process and a legal requirement in paediatric clinical trials, but it is impossible to define a common international legal framework on these topics, because of the different national regulations. Nev-

* Libera Università Maria Ss. Assunta (LUMSA). *E-mail*: l.nepi@lumsa.it. *The article was subject to a double-blind peer review process.*

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ertheless, from an ethical point of view we can delineate some common standards, concerning recruitment and decision-making, with special reference to the informed consent process. Yet, discrepancies appear also at ethical level about the weight of child's objection and the age thresholds.
This paper offers a narrative review of European and international rules of conduct with no legal binding force, such as guidelines, recommendations and opinions issued by European and international bioethics/research ethics committees, European institutions and international organizations and national bioethics committees in six selected countries (Austria, France, Germany, Italy, Spain and United Kingdom). Documents were collected by visiting the websites of relevant institutions.

2. The inclusion of minors in clinical trials

Children's vulnerability, due to incomplete physical and psychological development, is a preliminary question on every ethical discussion about paediatric clinical trials. Above all, there is a risk of harm because children are not able to protect themselves and this is highlighted by institutional documents. Beside the risk of health damage, there is a risk concerning protection of children's rights and proper acquisition of informed consent could become a legal and ethical issue. For these reasons, institutional documents highlight the importance of informed consent, risk assessment and inclusion criteria in clinical trials involving human subjects and these issues need to be developed carefully when dealing with minors, because they are not completely able to understand technical information and give consent freely[1].
In paediatric clinical trials the subject does not have full individual autonomy in the decision to be involved and a group of vulnerable people (minors and their families) needs to make decision in a context of uncertainty. Therefore, minors need appropriate support, not only from parents, but also from researchers and from the society as a whole. Specific protections are required and all institutional documents assume vulnerability as a major issue[2]. Vulnerability requires protection, but protection can restrict the right to participate in decision-making and to share benefits deriving from involvement in clinical trials. There is a tension between the need to avoid harm and the right to be informed and to be heard or to make choices.
In this regard, according to recent opinions issued by national and international institutions, children's participation in clinical trials is considered insufficient, in view of low involvement rates, so the balance has shifted to specifically encouraging children's inclusion in trials taking into account the benefit they can obtain, both direct and indirect[3]. Nuffield Council on Bioethics explicitly challenges the association between vulnerability and childhood, asking researchers to work in partnership with

[1] Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, 2016, Guideline 17; European Medicines Agency (EMA), *Guideline for Good Clinical Practice*, 2016.
[2] Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, 2016, Guideline 17.
[3] Working Party of research ethics committees in Germany, Ethische Aspekte der pädiatrischen Forschung, 2010; Austrian Bioethics Commission, *Research on persons without the capacity to consent-with special consideration of the concept of risk*, 2013; Nuffield Council on Bioethics, *Children and clinical research: ethical issues*, 2015.

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children and parents, not to protect children "from" research[4]. This implies that minors have to be supported to participate and to make decisions and their autonomy has to be respected as much as their integrity, giving importance to their views, listening to them and allowing them to contribute to decision-making. Nuffield Council on Bioethics affirms that children's welfare is a basic aspect to take into account, but its definition should encompass the possibility to contribute to scientific knowledge that could be useful for all children in the future[5]. That does not imply a moral duty to consent for children and parents, but only another aspect to be taken into account in determining what is good for children.

Institutional documents ask to involve children in research, first of all, for scientific reasons[6]. It is important to involve in research people unable to consent, and also children, in order to enable them to access benefits for their own health, balanced with related risks. Yet, from an ethical point of view, their involvement in clinical research has not to be viewed as necessary evil[7]. The classic approach claimed that minors' involvement in clinical research would not be suggested if trials could be carried out with adult subjects. If deemed necessary, researchers would have to include, first of all, less vulnerable subjects[8]. In recent years, the ethical evaluation has shifted to encouraging minor's involvement, but concerning the order of involvement in research, it is yet preferable to conduct research on adults before children. The WHO Research Ethics Review Committee[9] states that, before seeking consent and assent to involve children in research, it must be demonstrated that comparable research cannot be done with adults to the same effect and scientific impact. Older children having more capacity to consent should be involved before younger children, unless there are thorough scientific reasons to involve them before[10].

3. The balance between risks, burdens and benefits (direct and indirect)

Since clinical trials involving minors have allowed a great increase in therapeutic and diagnostic opportunities, their exclusion is currently considered unjustified. Nevertheless, clinical trials are structurally uncertain, because they are built on a scientific hypothesis, which needs to be confirmed through investigation, thus risks for children have to be considered. The protection of children in this field is now conceived as risk and burden minimization, rather than as exclusion. Hence, researchers

[4] Nuffield Council on Bioethics, *Children and clinical research: ethical issues*, 2015, paragraph 4.59.
[5] Nuffield Council on Bioethics, *Children and clinical research: ethical issues*, 2015, paragraph 4.28.
[6] European Medicines Agency (EMA), *Ethical considerations for clinical trials on medicinal products conducted with paediatric population*, 2008, 4.
[7] Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, 2016, Commentary on Guideline 17.
[8] European Medicines Agency (EMA), *Ethical considerations for clinical trials on medicinal products conducted with paediatric population*, 2008, 5.
[9] World Health Organization (WHO) Research Ethics Review Committee, *The Process of Seeking Informed Consent. Information for Researchers Concerning Informed Decision Making*, 2017.
[10] Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, 2016, Commentary on Guideline 17.

have to minimize risks and burdens, balancing these factors with expected benefits for subjects involved and improvement of knowledge[11].

Risk assessment is a fundamental aspect of a research protocol. In paediatric clinical trials, it requires strict control. Major risks in clinical trials are related to the health of involved subjects and data reliability. Health-related risks depend on prior experiences with the intervention/product to be tested and its nature. If the risk is minimal, compared to normal clinical treatment, children can be involved taking into account all the benefits they can get. These benefits can be distinguished as direct and indirect: the direct benefit is the consequence of a treatment on the patient's condition in terms of health recovery; the indirect benefit enables general findings to be obtained for medicine about the condition of a certain group of persons, to which the patient belongs, or general information useful to society[12].

General knowledge produced through the investigation can be usefully applied to a group of patients to which the person involved belongs and this is really important in research involving children, because benefits can be related to groups of people in an age category and not only to groups of people suffering from the same illness. When the benefit is referred to society as a whole, the ethical assessment needs to be stricter and it is important to evaluate the risk factor: the risks must be minimized and no more than minimal[13].

In addition to risk, burden of research participation for minors has to be considered as an important factor, more than in clinical trials involving adults. It can concern anxieties, pain or interference in children's everyday lives, such as being separated from parents during the trial, frequent invasive procedures or burdensome side effects. Parents are usually more focused on risks for life and health of their children, but burdens can have harmful effects, which have to be taken into account. Burden perception is not objective and depends on individual feelings, but the burden minimization has to be pursued by researchers and to be taken into account by Research Ethics Committees. Overall pain is an important factor to consider in paediatric clinical trials, even though difficult to predict or assess, because it can affect the child's neurological, psychological and physical development[14].

Another important issue related to risks and benefits is the use of placebo in paediatric clinical trials. According to WMA[15], the use of placebo is justified only for scientific reasons and with the informed

[11] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), E 11: *Clinical investigation of medicinal products in the* paediatric *population*, 2000; World Health Organization (WHO), *Standards and operational guidance for ethics review of health-related research with human participants*, 2011; European Commission, *Report from the Commission to the European Parliament and the Council. Better Medicines for Children – From Concept to Reality*, 2013; Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, 2016.

[12] French National Consultative Ethics Committee for Health and Life Sciences, *Transposition en droit français de la directive européenne relative aux essais clinique des medicaments: un nouveau cadre éthique pour la recherché sur l'homme*, 2003, 3-5.

[13] Austrian Bioethics Commission, *Research on persons without the capacity to consent-with special consideration of the concept of risk*, 2013, 40; Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, 2016, Guideline 17.

[14] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), E 11: *Clinical investigation of medicinal products in the paediatric population*, 2000, 12.

[15] World Medical Association (WMA), *Declaration of Helsinki* (as amended), 2013, art. 33.

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consent of the patient, but should be restricted in paediatric clinical trials, because randomization and procedure's risks are not easily understood by parents and children. Placebo should not be used if effective treatments are available.

Exploitation of people unable to consent is unacceptable and a mandatory ethical review by ethics committees is an essential requirement[16]. Research integrity also needs to be considered, to guarantee compliance with ethical principles and professional standards[17]. Research ethics committees have an important role in protocols review and their focus is on the "ethical acceptability" of the research[18]. Dealing with paediatric trials, research ethics committees need to have specialist expertise on children healthcare to assess adequately risks and burdens of the envisaged procedures. The scrutiny process involves both scientific and ethical aspects, thus an adequate ethical and peer review is required. Failure to follow ethical guidelines implies that Ethics Committees or competent authorities do not give permission to proceed.

4. The role of parents

The role of parents is very important, both from a legal and an ethical point of view. It cannot be interpreted only as a right to decide or a duty to protect, but also as assistance and support to children's evolving autonomy. Parental decisions should evaluate the "child's best interest", a complex concept determined on a case-by-case basis, considering individual needs and rights. Indeed, since clinical trials are not only focused on the participant's interests, Nuffield Council on Bioethics[19] affirms that parental consent to research "should be based on their confidence that participation in the proposed research is compatible with their child's immediate and longer term interests". This is a proposal to avoid that the minor's "best interest", fundamental in clinical practice, overrides other ethical values and becomes the only issue to consider in decision-making.

Parents need to be supported in decision-making, overall if decision has to be taken in difficult situations and trials imply burdens or risks. In cases of serious illness or when parents begin to deal with a child's illness, distress could compromise the parental capacity of judgement. Parents could need to consult their child's physician about the chance to participate in a clinical trial. If the investigator is also the physician, particular attention needs to be paid to undue influence and conflict of interests: willingness to participate in a clinical trial cannot be influenced by the concern to be undermined in normal access to care. If the researcher is also a clinician in charge of providing care to the minor involved in a clinical trial, commitment to investigate cannot override the duty to care and the interest in the success of research cannot compromise the patient's interest to be properly treated[20].

[16] Council of Europe, Committee on Bioethics (DH-BIO), *Guide for Research Ethics Committee Members*, 2012, 40.
[17] European Group on Ethics in Science and New Technologies (EGE), *Statement on the formulation of a code of conduct for research integrity for projects funded by the European Commission*, 2015.
[18] World Health Organization (WHO), *Standards and operational guidance for ethics review of health-related research with human participants*, 2011, 12.
[19] Nuffield Council on Bioethics, *Children and clinical research: ethical issues*, 2015, paragraph 4.33.
[20] Nuffield Council on Bioethics, *Children and clinical* research*: ethical issues*, 2015, xxxiii.

If parental permission is impossible to obtain and the study is emergency research, investigators can ask an approval to the ethics review committee and must inform and involve parents as soon as possible, but if the minor is able to understand and decide, his/her decision should be respected[21].

5. Children and mature minors: different age, different issues

To be minor is a legal status and the age of adulthood is conventionally fixed by the law. To be a child or young is an existential condition and there are great differences between infants, children and young people. Minors' continuous development is actually an ethical issue: "What is more difficult and especially deserves 'ethical weighing' is research on children as children continually develop their ability to give consent as they grow older"[22].

All the institutional documents affirm that as age advances, maturity and capacity to understand become more relevant, as well as the importance of individual autonomy. Considering the ethical value of the minor's will, some documents propose an age-based classification. ICH distinguishes newborns (0 to 27 days); infants and toddlers (28 days to 23 months); children (2 to 11 years); and adolescents (12 to 18 years). In the same document ICH states that "any classification of the paediatric population into age categories is to some extent arbitrary", but however useful to think about the study design[23].

EMA makes no distinction between minors and children, using these terms as synonyms[24]. Nevertheless, the document deals with the issue of consent and its value according to age groups and the subject's level of maturity: for children from birth to 3 years, it is impossible to obtain a valid assent; from 3 to 6 years, there is no specific indication, whereas for children of school age (from 6 years) information and obtaining of assent is recommended; children from the age of 9 are considered able to better understand the information; adolescents are more independent and need respect for their autonomy, not only protection: "Assent from an adolescent who is a minor should be sought, and, where possible respected"[25]. Researchers must however assess that adolescents have understood the information provided.

If research implies minimal risks and minimal burden for minors involved, Austrian Bioethics Commission[26] asks for parental permission only for children up to the age of 14.

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[21] NUFFIELD COUNCIL ON BIOETHICS, *Children and clinical research: ethical issues*, 2015, paragraph 6.35; ITALIAN COMMITTEE FOR BIOETHICS, *Clinical trials in adult or minor patients who are unable to give informed consent in emergency situation*, 2012.

[22] AUSTRIAN BIOETHICS COMMISSION, *Research on persons without the capacity to consent-with special consideration of the concept of risk*, 2013, 44;

[23] INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE (ICH), E 11: *Clinical investigation of medicinal products in the paediatric population*, 2000, 7.

[24] EUROPEAN MEDICINES AGENCY (EMA), *Ethical considerations for clinical trials on medicinal products conducted with paediatric population*, 2008, 7.

[25] EUROPEAN MEDICINES AGENCY (EMA), *Ethical considerations for clinical trials on medicinal products conducted with paediatric population*, 2008, 12.

[26] AUSTRIAN BIOETHICS COMMISSION, *Research on persons without the capacity to consent-with special consideration of the concept of risk*, 2013, 46.

Dealing with the broad concept of "childhood", Nuffield Council on Bioethics[27] distinguishes three different situations without fixing rigid age thresholds instead:

1. Case One: children who are not able at this time to contribute their own view as to whether they should take part in research, such as babies and very young children, or children who are temporarily unable to contribute because they are so unwell or are unconscious.
2. Case Two: children who are able at this time to form views and express wishes, but who are clearly not yet able to make their own independent decisions about research involvement.
3. Case Three: children and young people who potentially have the intellectual capacity and maturity to make their own decisions about taking part in a particular research study, but who are still considered to be minors in their domestic legal system.

All children will be included in case one at the beginning of life. When a child can be included in Case Three, his/her assent has a particular weight, comparable to an actual informed consent.

According to CIOMS "As adolescents near the age of majority, their agreement to participate in research may be ethically (though not legally) equivalent to consent. In this situation, parental consent is ethically best considered as 'co-consent' but legally, the adolescent's agreement remains assent. If child or adolescent participants reach the legal age of majority according to applicable law and become capable of independent informed consent during the research, their written informed consent to continued participation must be sought and their decision respected"[28].

In long-term trials, investigators should periodically check minor's maturity and capacity to consent and seek their assent or informed consent, if deemed appropriate, or once the subject reaches the legal age to consent[29].

6. Assent and parental permission

To be legally and ethically justified, clinical trials need to be freely accepted by the subjects involved, on the basis of adequate information about relevance, purpose, risks and burdens of the envisaged procedures. Subjects must have a clear idea that they are going to be involved in research and not in normal clinical care, even though some benefits are expected[30].

In paediatric clinical research, the informed consent process requires parental permission and child's assent. According to WHO Research Ethics Review Committee[31] obtaining informed consent in paediatric clinical trials should follow some essential rules:

[27] NUFFIELD COUNCIL ON BIOETHICS, *Children and clinical research: ethical issues*, 2015, paragraph 4.5.

[28] COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, 2016, Commentary on Guideline 17.

[29] EUROPEAN MEDICINES AGENCY (EMA), *Ethical considerations for clinical trials on medicinal products conducted with paediatric population*, 2008, 10; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Addendum to E 11: *Clinical investigation of medicinal products in the paediatric population* (Step 1 version), 2016.

[30] COUNCIL OF EUROPE, COMMITTEE ON BIOETHICS (DH-BIO), *Guide for Research Ethics Committee Members*, 2012; WORLD MEDICAL ASSOCIATION (WMA), *Declaration of Ottawa on Child Health* (as amended), 2009; UNESCO INTERNATIONAL BIOETHICS COMMITTEE, *Report On Consent*, 2008.

[31] WORLD HEALTH ORGANIZATION (WHO) RESEARCH ETHICS REVIEW COMMITTEE, *The Process of Seeking Informed Consent. Information for Researchers Concerning Informed Decision Making*, 2017.

- According to the Convention on the Rights of the Child, "child" means "every human being below the age of eighteen years unless under the law applicable to the child, majority is attained earlier".
- Once it has been determined that the research should be permissible, researchers must obtain parental/guardian consent on an informed consent form for all children.
- Children sufficiently able to understand the proposed research should have the opportunity to be informed about the research, to have their questions and concerns addressed and to express their agreement or lack of agreement to participate.
- While the age at which this informed assent should be taken varies, researchers should consider asking for assent from children over the age of seven years with assent taken from all children over the age of twelve years.
- Children express their agreement to participate on an informed assent form written in age appropriate language. This form is in addition to, and does not replace, parental consent on an informed consent form.
- Assent which is denied by a child should be taken very seriously.

Indeed, minors have no legal capacity to give informed consent to be involved, but they are not completely unable to understand and they gradually mature and develop their capacity to make autonomous decisions. Nonetheless, their participation in decision-making is pivotal to ensure respect for their dignity, even though they are not entitled to give an actual informed consent. Hence, they can be involved in decision-making process giving an "assent" to research, but this term has different meanings[32], depending on the context and on the minor's age. Its purpose is to facilitate a context in which minors can cope with distress, be involved in decisions, be heard and considered about their wishes and concerns. According to EMA "assent should be understood … as the expression of the minor's will to participate in a clinical trial"[33].

Ethical guidelines often require documentation of assent and in some cases place great value upon it: "The processes for informing the child and seeking assent should be clearly defined in advance of the research and documented for each child"[34]. Through the assent engagement of minors can be assured in the research discussion and in decision-making, depending on their individual capabilities. Familiar context and personal circumstances should also be taken into account. In cases of chronic disease, minors can have more experience and capacity than the parents to understand risks, burdens and benefits of a clinical trial.

Nuffield Council on Bioethics distinguishes three different situations (see above) to highlight that in some cases children are unable to participate in decision-making, but in other cases they can be involved to contribute with their view, or even decide independently. In Case One, assent has no value, but in Case Two it should be balanced with parents' views to determine risks, benefits and burdens, taking into account the child's maturity and capacity to understand. In Case Three, young children

[32] Spanish Bioethics Committee, *Informe del Comité de Bioética de España sobre el proyecto de Real Decreto de ensayos clínicos*, 2013, 15-16.

[33] European Medicines Agency (EMA), *Ethical considerations for clinical trials on medicinal products conducted with paediatric population*, 2008, 8.

[34] European Medicines Agency (EMA), *Ethical considerations for clinical trials on medicinal products conducted with paediatric population*, 2008, 11.

can potentially make decisions for themselves, even if parents still have moral and legal duties to protect them.

As the minor is not entitled to provide a full legally binding informed consent, an authorization has to be provided by parents, after adequate information. Parents need time and detailed information to decide, because they bear responsibilities for their children and not only for themselves. They might need to talk with their child on their own, after being informed, and researchers should not take part in the decision-making. Family members must be free from undue pressure and be informed of the possibility to revoke informed consent without any prejudice for their children's care.

Parental permission and assent should be obtained at the same time. Informed consent should be obtained from the subject involved once he/she reaches the age of consent, because parental permission and assent have not the same value as the consent given by an adult. Children who are wards need an advocate's assistance. The Italian *Codice dei diritti del minore alla salutee ai servizi sanitari*[35] provides that the minor has the right to consent or disagree and personally sign the informed consent together with the legal representative.

Research protocols can also be designed for emergency situations, involving patients unable to consent (e.g. sepsis, head trauma or stroke). In such circumstances, researchers must try to talk with a legal representative to obtain consent as soon as possible, but if a substitute is impossible to contact, the research can be carried out only if an ethics committee has previously given the authorization to proceed without consent. This authorization has to be obtained when the research protocol is approved, because it concerns circumstances in which a decision must be taken quickly. In evaluating the protocol, an ethics committee must assess a sound scientific background and likelihood of benefit for the subject. Risks associated to the trials have to be reasonable and previously expressed wishes concerning involvement can be taken into account[36]. Italian Committee for Bioethics recommends the constitution of *ad hoc* independent ethics committees for clinical trials in emergency situations[37].

7. Objection from the child

According to EMA "Strong and definitive objections from the child should be respected"[38] and especially when no direct benefit is prospected by researchers. Some exceptions are proposed by ICH, exclusively in view of potential benefits: "Although a participant's wish to withdraw from a study must be respected, there may be circumstances in therapeutic studies for serious or life-threatening diseases in which, in the opinion of the investigator and parent(s)/legal guardian, the welfare of a pae-

[35] Istituto Nazionale per i Diritti dei Minori (INDiMi), *Codice dei diritti del minore alla salute e ai servizi sanitari*, 2012, art. 14.

[36] Council for International Organizations of Medical Sciences (Cioms), *International Ethical Guidelines for Health-related Research Involving Humans*, 2016, Guideline 16.

[37] Italian Committee for Bioethics, *Clinical trials in adult or minor patients who are unable to give informed consent in emergency situation*, 2012.

[38] European Medicines Agency (Ema), *Ethical considerations for clinical trials on medicinal products conducted with paediatric population*, 2008, 13.

diatric patient would be jeopardized by his/her failing to participate in the study. In this situation, continued parental (legal guardian) consent should be sufficient to allow participation in the study"[39].
In dealing with children's "deliberate objection", CIOMS equally highlights the importance of child's wishes in decision-making, but asks to consider expected benefits. A deliberate objection should be respected "even if the parents have given permission, unless the child or adolescent needs treatment that is not available outside the context of research, the research intervention has a clear prospect of clinical benefit, and the treating physician and the legally authorized representative consider the research intervention to be the best available medical option for the given child or adolescent. In such cases, particularly if the child is very young or immature, a parent or guardian may override the child`s objections"[40].
Conversely, child's objection has more value than parental permission when research has no direct benefit for the subjects involved. Silence or absence of objection cannot be considered as assent[41].
Consent can be withdrawn at any time, also during a procedure, unless when there is a serious danger for the subject's health. Withdrawal of consent does not provoke the end of relationships between the researchers and the subjects involved[42].
If assent and parental permission are impossible to obtain, the consent can be waived, but this waiver needs to be approved by an independent research ethics committee. CIOMS[43] requires some conditions to approve a consent waiver:

- the research would not be feasible or practicable to carry out without the waiver;
- the research has important social value; and
- the research poses no more than minimal risks to participants.

8. Shared decision-making: from a legal point of view to an ethical perspective

Professionals interacting with children and families need to have both technical and non-technical skills to communicate adequately. The role of ethics review committees is also important in improving children's participation in clinical trials: the action of these bodies could be not only protective, but also facilitative, as highlighted by Nuffield Council on Bioethics[44] that emphasizes the ethical value of paediatric research.
Nevertheless, to be ethically justified, clinical research involving minors must consider the concepts of "minimal risk" and "best interest" of the child, because the risks must be minimized and no more than minimal. Usually "minimal risk" means that the probability and magnitude of harm or discom-

[39] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), E 11: *Clinical investigation of medicinal products in the paediatric population*, 2000, 11.
[40] Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, 2016, Commentary on Guideline 17.
[41] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Addendum to E 11: *Clinical investigation of medicinal products in the paediatric population* (Step 1 version), 2016, 5.
[42] European Medicines Agency (EMA), *Ethical considerations for clinical trials on medicinal products conducted with paediatric population*, 2008, 11.
[43] Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, 2016, Guideline 10.
[44] Nuffield Council on Bioethics, *Children and clinical research: ethical issues*, 2015, xxv.

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fort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological activity. The "best interest" approach generally promotes an effort to be more objective in balancing risks and benefits, weighing them in the specific situation regardless of individual wishes. In the case of clinical research, however, the concept is too generic, since the balance between risks and benefits is undefined and it is hard to define the child's best interest in a situation of clinical uncertainty.

Therefore, in the research setting a certain emphasis on autonomy seems to be justified because of the consequent risks and subjects may be granted a higher level of autonomy than in clinical practice, where it is instead appropriate to give greater weight to the best interest of the minor. Yet, to prevent a conflict of autonomies between children and parents, the Nuffield Council on Bioethics recommends to adopt the "Shared decision-making" approach, emphasizing the importance of a partnership between researchers, families and children, to avoid the idea of informed consent as a parental permission cancelling or reducing professional responsibilities and the importance of minors' involvement. Parental permission should not be considered as conclusive as an informed consent given about an adult's own participation in clinical trials and the assent is not an independent event. Since the individual autonomies could collide, it is important to seek protection for the family as a whole. Hence the ethical importance of shared decision-making, to adopt a global perspective about families and their autonomy. The researcher's role is crucial to facilitate shared decision-making, notably when conflicts arise between family members about the children's involvement in research. They should assess when family members do not communicate well and give parents and children enough time to ask questions and think about the alternatives. That is why it would be important for researchers to have communication skills and knowledge about children's psychology and family counselling.

If disagreement between family members is impossible to solve, it is difficult to choose who to listen to. In these cases, it is not clear if the child's objection to research is binding. If shared decision-making should be assumed as a major value, disagreement would become a barrier to the informed consent acquisition. In this case, Nuffield Council on Bioethics[45] (2015, paragraph 6.24-6.25) recognizes determinative value to dissent, both expressed by parents or by children. By affirming that, Nuffield Council of Bioethics shifts from a formal concept of informed consent, as legal requirement, to an ethical approach to the process, seen as an instrument to facilitate an agreement between different persons to share goals and benefits. This different point of view deserves consideration as a way to prevent conflicts and assure a proper involvement of minors and their families in clinical trials.

[45] NUFFIELD COUNCIL ON BIOETHICS, *Children and clinical research: ethical issues*, 2015, 6.24-6.25.

Special issue

Gender and Informed Consent in Clinical Research: Beyond Ethical Challenges

Loredana Persampieri*

ABSTRACT: Informed consent for clinical research is both a communication process and a document to inform individuals about relevance, scope, benefits and risks of their involvement in research and to obtain consent for participation in a study. Critical issues arise when the research involves particularly vulnerable subjects, such as women in some circumstances (i.e. specific physiological conditions, namely, fertility, pregnancy, breastfeeding, or socio-economic vulnerabilities). If, on one hand, participation of particularly vulnerable subjects in clinical research requires special care and safeguards to protect the person's rights and reduce risks of undue inducement and therapeutic misconception; on the other, a vulnerability-based exclusion would result in discrimination and a barrier to possible health benefits deriving from advances in scientific research. In this context, gender-related issues may become a huge challenge in terms of appropriateness, completeness and clarity of information and freedom of consent. This article will explore ethical issues surrounding women's participation in clinical research, with a specific focus on gender considerations in informed consent, through a narrative review of soft law at the European level and beyond on this topic. Concerns on the role of the male/female partner in the informed consent process will also be addressed.

KEYWORDS: Informed consent; vulnerability; gender; fertile women; pregnant/breastfeeding women

* *Ph.D, Libera Università Maria Ss. Assunta (LUMSA), Rome. E-mail: l.persampieri@lumsa.it.* *The article was subject to a double-blind peer review process.*
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1. Introduction

Autonomy of a subject in the decision to participate in clinical research is of major importance, being the informed consent the document that allows an individual to voluntarily decide whether or not to enrol in a clinical study. However, relevant issues arise when the research involves particularly vulnerable subjects, such as women in some situations (i.e. specific physiological conditions, namely, fertility, pregnancy or breastfeeding, or socio-economic factors affecting their freedom and self-determination). Gender[1] issues in communication and understanding of the potential benefits and risks related to any clinical study can seriously challenge the appropriateness, completeness and clarity of information and of obtaining informed consent. Hence, a participant-tailored approach to communication is required for an effective consent process.

There are very few International and European guidelines and recommendations focusing on a gender-tailored approach to informed consent, in terms of effective communication strategies to facilitate understanding of benefits and risks related to particularly vulnerable subjects' involvement in clinical research. Scattered references to this topic can be found in documents addressing women's participation in clinical trials or in ethical guidelines for research involving human subjects: in this context, it is possible to devise a number of common ethical standards, as well as problematic issues where disagreement or gaps still remain. However, particular attention is devoted to raising awareness on safety methods and identifying special sections within consent forms with inclusion/exclusion criteria relating to pregnant/breastfeeding women or of childbearing potential. There is often consideration for cultural or social aspects, which may lead to gender vulnerabilities, but these observations are not translated in specific procedures to be implemented in the informed consent process.

This article provides a narrative review of guidelines, recommendations and opinions issued by International Organizations, European institutions, International and European bioethics/research ethics committees, scientific societies, national bioethics/research ethics committees in selected countries (Austria, Belgium, France, Germany, Italy and United Kingdom). The analysis is not limited to the European context, but it is also extended to the United States, with regard to topics which are still not clearly defined (i.e., how to improve access of women in clinical research) and thus needing further analysis. Moreover, Canada was taken into account as an illustrative case, due to interesting developments with regard to gender considerations in the informed consent process. Resources were gathered by monitoring the websites of key International, European and national bodies in this field.

[1] In this article, the word "sex" will be used to refer to the biological dimension (sexual difference between males and females) and "gender" for the psychological, social and cultural dimensions, which influence men and women's behaviours in their decision to participate in clinical research, requiring a differentiated approach in the informed consent process. The two words are confused and often overlap in soft law. The evolution in the notion of gender beyond sexual binarism (the so-called gender or post-gender theories or ideologies) will not be taken into account in this context, as it does not pertain to the object of this review.

2. Women as research actors and participants

At the European level, not many guidelines shed light on the relationship between the protection of women's health and the need for "gender-oriented clinical trials": up to date, very few National Bioethics Committees in Europe have addressed this topic by developing a thorough reflection on the shortcomings of a low-rate participation of women in research, with a clear emphasis on the benefits and risks of their inclusion/exclusion from clinical research. In Italy, the Italian Committee for Bioethics (NBC) raised awareness on this issue in its *Opinion on Pharmacological Trials on Women*[2], in which it focused on the state-of-the-art of pharmacological experimentation from a gender perspective and highlighted key bioethical problems in this field, within the context of avoiding any form of discrimination and promoting gender equality in healthcare and research. The issues relating to pharmacological experimentation on pregnant women were not considered in the scope of the document. The NBC stressed that in clinical research women are referred to as "weak subjects", or at least they seem to be not subjected to adequate consideration, which should take into account their specificity both from a quantitative point of view (rates of women enrolled in trials compared to men) and a qualitative point of view (data analysis with regard to sexual differences)[3]. Moreover, the Opinion discussed interesting outcomes concerning a number of studies being conducted in Italy on female pathologies, where the involvement of women is directly linked to the nature of the pathology. The data provided by the Italian Observatory on drug experimentation showed a progressive increase in studies specifically carried out on women, especially in phases II and III. However, women's involvement is mainly identified in relation to therapeutic strategies for specifically female diseases, such as breast cancer and the control of the post-menopausal osteoporosis. There are other areas in which the NBC devised a lack of pharmacological trials on female pathologies as well: particularly with regard to the substitutive hormonal treatment in postmenopausal women, where there are many risks of heart attack or breast cancer or cardiovascular toxicity of the chemotherapy drugs used to treat breast cancer. Although, the most critical under-representation is identified in those trials on drugs for diseases affecting both men and women: clinical research falls short on considering women's specific biological traits and their changing health condition, with a higher risk of suffering medication side effects. This is due to sex-based differences in pharmacokinetic and pharmacodynamics characteristics of drugs. Many researchers have not devoted adequate efforts to look into sexual differences relevant for the study of symptoms, assessment of diagnosis and efficacy of treatments. In this regard, the Italian Committee set out a number of bioethical recommendations, which recalled the importance of implementing the key "ethical principle of fairness of a pharmacological trial on both men and women, in real conditions of equality, without unjustified exclusion, while stressing the necessity of identifying and removing the causes of this unfairness"[4]. Along with considering specific age-related vulnerabilities in pharmacological trials, it is equally fair and right to place the same emphasis on gender differences, which are likely to lead to diverse research results and require tailored trial approaches. The NBC called for an increased level of women participation in research, es-

[2] ITALIAN COMMITTEE FOR BIOETHICS (NBC), *Opinion on Pharmacological trials on women*, 2008.
[3] ITALIAN COMMITTEE FOR BIOETHICS (NBC), *Opinion on Pharmacological trials on women*, 2008, p. 7.
[4] ITALIAN COMMITTEE FOR BIOETHICS (NBC), *Opinion on Pharmacological trials on women*, 2008, p. 17.

pecially in studies aimed at better understanding women health conditions (i.e. common diseases, specific risk factors etc.), taking into account changes in the their psychological, social and cultural conditions, in order to devise gaps in those areas of the health care system where new and variable female needs are poorly taken care of. It also pointed out that an improved involvement of women would guarantee an effective condition of equality of care with respect to men, since a lack of sex-differentiated data results in a form of discrimination for women's health. According to the Italian Committee, the promotion of women's participation in clinical research should rely on providing adequate information on the negative consequences deriving from a lack of differentiated trials, as well as on the social importance of their enrolment in clinical research. Another way to devote greater attention to gender issues in trials is to foster the involvement of women as research actors (both as researchers and representatives of patient associations) and in ethics committees, so as to enable their active participation in the definition of research protocol procedures and, most interestingly, in the informed consent process. In this context, the Austrian Bioethics Commission at the Federal Chancellery published, in 2008, *Recommendations with Gender Reference for Ethics Committees and Clinical Studies*, in which it provided guidance on how to ensure a gender balance in the composition of ethics committees and identified a number of requirements for a gender approach to clinical research[5]. There are no specific recommendations regarding a differentiated approach to informed consent for women and men. It only emphasizes the need for an ethics committee to assess the appropriateness of the method of obtaining informed consent.

As for European soft law, reference is made to women's peculiarities in the general context of health, however, clear and specific guidelines or policies focusing on inclusion/exclusion criteria for women in clinical research (beyond reporting the lack of gender-based stratified data in this area) have not been issued yet. Among the awareness-raising guidelines, it is noteworthy to recall the *Note for Guidance on General Considerations for Clinical Trials*, published by the European Medicines Agency (EMA) in 1998, highlighting that "women of childbearing potential should be using highly effective contraception to participate in clinical trials"[6]. In 2003, based on the conclusions of a European working group including female researchers and representatives of the pharmaceutical industries, it issued the *Note for Guidance on the Clinical Development of HIV-Medical Products*[7] in which the EMA made recommendations for envisaging study protocols pointing out gender-based data analysis with a male-female comparative approach, alongside calling for statistically significant women's enrol-

[5] The Austrian Bioethics Commission recommended that "action be taken to: 1) ensure an even balance of the sexes in the composition of ethics committees and that such measures be applied equally with regard to all legally required representatives in an ethics committee; 2) guarantee the inclusion of men and women of all ages according to acknowledged scientific principles (prevalence of the disease) in all biomedical and other research projects and to accept the exclusion of women of childbearing potential in exceptional cases only.; 3) ensure that the inclusion of women of childbearing potential in clinical trials (with due consideration to international guidelines) be formulated and discussed and that rules be provided which make provision for a women-friendly study design of the projects that are submitted"; 4) it also stressed that "the exclusion of women or men of any age from clinical trials should require a detailed justification". See AUSTRIAN BIOETHICS COMMISSION, *Recommendations with Gender Reference for Ethics Committees and Clinical Studies*, 2008, paragraphs 18, 20-22.

[6] EUROPEAN MEDICINES AGENCY (EMA), *Note for Guidance on General Considerations for Clinical Trials*, 1998, p. 11.

[7] EUROPEAN MEDICINES AGENCY (EMA), *Note for Guidance on the Clinical Development of HIV-Medical Products*, 2003.

ment and appropriate medical training adapted to this protocol design. In 2005, the EMA published *ICH-Gender considerations in the conduct of clinical trials*, which reviewed the International Conference on Harmonization (ICH) guidelines dealing with women issues[8]. The EMA stressed the fact that "while women appear to be participating in all phases of study development, participation is lower in early phases (phase 1 – 1 / 2)"[9]. Although, these trials are important for determining safety, efficacy and changes in dosage based on gender effects. Nevertheless, unlike special consideration for age-related specificities in other documents, it argued against "the need for a separate ICH guideline on women as a special population in clinical trials", and stated that "relevant ICH[10] and regional guidelines should be consulted for guidance on demographic considerations, including gender, in the design, conduct and analysis of clinical trials", while stating that "this issue may be revisited if future experience suggests a change from current practice"[11]. Considerations on relevant information to be included in a gender-based informed consent process are not provided.

The European Parliament adopted a Resolution of 14 February 2017 on promoting gender equality in mental health and clinical research (2016/2096 (INI)), which noticed that although the European Medicines Agency (EMA) recognized the importance of taking into account sex-related differences in drug response, it has not developed specific strategies aimed at investigating these differences[12]. Therefore, it urged EMA to take action in this field by drawing up separate guidelines for women as a special population in clinical trials.

At the international level, guidance on women participation in research is embedded in the *International Ethical Guidelines for Health-Related Research Involving Humans (*as revised in 2016), prepared

[8] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), *Sex-related Considerations in the Conduct of Clinical Trials*, 2004 (revised in 2009).

[9] European Medicines Agency (EMA), ICH-*Gender Considerations in the Conduct of Clinical Trials*, 2005, p. 4.

[10] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), *ICH Harmonised Tripartite Guideline. E4*: *Dose-Response Information To Support Drug Registration*, 1994; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), *ICH Harmonised Tripartite Guideline. E3*: *Structure and Content of Clinical Study Reports*, 1995; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), *ICH Harmonised Tripartite Guideline. E8: General Considerations for Clinical Trials,* 1997; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), *ICH Harmonised Tripartite Guideline. E2E: Pharmacovigilance Planning*, 2004; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), *ICH Harmonised Tripartite Guideline. M3 (R2): Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals,* 2009; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), *ICH Harmonised Tripartite Guideline. E2C (R2): Periodic Benefit-Risk Evaluation Report*, 2012; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), *ICH Harmonised Guideline. M4E*: *The CTD – Efficacy Guidance for Industry* (as revised in 2017).

[11] European Medicines Agency (EMA), ICH-*Gender Considerations in the Conduct of Clinical Trials*, 2005, pp. 3-6.

[12] The European Parliament recognized that "specific strategies to implement guidelines for the study and evaluation of gender differences in the clinical evaluation of drugs have not been developed by the European Medicines Agency (EMA), despite the fact it has acknowledged that 'some of the factors that influence the effect of a medicine in the population may be important when considering potential differences in response between men and women' and that 'gender-specific influences can also play a significant role in drug effect". See *European Parliament resolution of 14 February 2017 on promoting gender equality in mental health and clinical research (2016/2096 (INI)).*

by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO). Guideline n° 18 focuses particularly on women as research subjects, informed consent and childbearing potential issues: it emphasizes the need to foster the inclusion of women in clinical research and protect their autonomy in the decision-making process, deeming individual informed consent an imperative requirement[13]. However, this last aspect may become problematic for those women with cultural backgrounds where the community dimension prevails over the individual one. Most likely, it will constitute a reason for reluctance to participate in clinical trials; hence, resulting in an exclusion criterion for specific population subgroups. This issue, as well as fertility and pregnancy aspects, will be further discussed later on.

In 2010, the Department of Gender, Women and Health (GWH) of the World Health Organization (WHO) published a document on *Gender, women and primary health care renewal*[14], which highlighted the fact that gender biases permeate health research through: 1) the lack of sex-disaggregated data; 2) designing research methodologies that are not tailored to gender and other social disparities; 3) methods used in clinical trials for new drugs that exclude women and girls from study populations and lack a gender perspective; 4) gender imbalance in ethical committees, research funding and advisory bodies; 5) differential treatment of women scientists[15]. It firmly argued that research failing to examine the role of sex and gender in health is both "unethical" and "unscientific". Moreover, the WHO underlined that individuals need to be given information to enable meaningful participation, not always through the written word, but by using communication modes that are suitable to women and men. Health literacy initiatives would constitute an important component of empowerment.

[13] Guideline n° 18 states that "women must be included in health-related research unless a good scientific reason justifies their exclusion. Women have been excluded from much health-related research because of their child-bearing potential. As women have distinctive physiologies and health needs, they deserve special consideration by researchers and research ethics committees. Only the informed consent of the woman herself should be required for her research participation. Since some societies lack respect for women's autonomy, in no case must the permission of another person replace the requirement of individual informed consent by the woman". See COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, 2016, Guideline n°18, p. 69.

[14] WORLD HEALTH ORGANIZATION (WHO) Department of Gender, Women and Health (GWH), *Gender, women and primary health care renewal: a discussion paper*, 2010. For an overview of WHO's work on the issues related to women and health, see also: WORLD HEALTH ORGANIZATION (WHO), *Guidelines for Good Clinical Practices (GCP) for trials on pharmaceutical products*, 1995a; WORLD HEALTH ORGANIZATION (WHO), *Women's Health: improve our health, improve our world* (WHO Position Paper, Fourth World Conference on Women), 1995b; WORLD HEALTH ORGANIZATION (WHO), Women's Health and Development Family and Reproductive Health, *Gender and Health: Technical Paper,* 1998; WORLD HEALTH ORGANIZATION (WHO*), Standards and operational guidance for ethics review of health-related research with human participants*, 2011.

[15] The WHO also stressed that "in the European Union, efforts at including the gender perspective into health research had been effective with regard to increasing women participation in science (research by women), but not as effective in tackling problems of research for and about women". See WORLD HEALTH ORGANIZATION (WHO) Department of Gender, Women and Health (GWH), *Gender, women and primary health care renewal: a discussion paper*, cit., p. 49.

3. Fair inclusion of women in clinical research: the US experience

The report *Women's Health Research: Progress, Pitfalls, and Promise* issued by the US Institute of Medicine. Committee on Women's Health Research (2010) reviews the process of exclusion/inclusion of women with regard to clinical research in the United States[16]. In 1977, the Food and Drug Administration (FDA) excluded women of childbearing potential from participating in phase I and early phase II trials, because of thalidomide and diethylstilboestrol tragedies. This was meant to avoid the possibility of exposing a foetus to a drug that had not satisfied preliminary safety and efficacy testing. Therefore, women of childbearing potential were allowed to participate in clinical trials only after evidence of a drug's effectiveness in humans was obtained (that is, in late phase II and phase III trials) and following data analysis from animal reproductive studies to check whether the drug caused birth defects; yet, women resulted in being underrepresented in the later phases as well.

In 1985, the Public Health Service Task Force on Women's Health Issues concluded that "the historical lack of research focus on women's health concerns had jeopardized the quality of health information available to women and the health care they receive"[17]. From the publication of that report, there have been pivotal changes in women's health research, especially with regard to government support, policy and regulations leading to the development of new scientific knowledge about women's health. This commitment was heightened by the establishment of specific offices on women's health in several government agencies. In 1986, the National Institutes of Health (NIH) designed a policy, which recommended for the inclusion of women in clinical research. Alongside Government reports, also documents from other organizations, including the Institute of Medicine (IOM), have emphasized the need to foster and monitor women participation in health research. Previously, little clinical research on women's health had been carried out, due to existing concerns about risks of possible foetal exposure to an experimental substance, the variability in hormonal status in women, comorbidities and legal issues. Nevertheless, perplexities remained that if FDA approved drugs on the basis of clinical trials in which women were underrepresented, their effectiveness and safety in women would not be known. In 1993, the NIH Revitalization Act basically strengthened existing NIH policies, but with a number of key changes: *inter alia*, the necessity of fulfilling the requirement for inclusion of adequate numbers of women, in order to guarantee a valid analysis by sex for phase III trials and detect differences in intervention effects, while making clear that cost should not be allowed as an acceptable reason for excluding this population group. In the same year, the FDA reversed its 1977 guidelines barring women of childbearing potential from participating in clinical research and published a *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*. The Guideline focused on the inclusion of women in clinical research under specific criteria and a sex-based analysis of data[18]. The Committee on Women's Health Research noticed

[16] U.S. INSTITUTE OF MEDICINE, Committee on Women's Health Research, *Women's Health Research: Progress, Pitfalls, and Promise,* Washington (DC), 2010.

[17] U.S. INSTITUTE OF MEDICINE, Committee on Women's Health Research, *Women's Health Research: Progress, Pitfalls, and Promise*, cit., p. 1.

[18] The FDA Guideline hinged upon "1) encouraging inclusion of women in phase I and II studies; 2) requiring inclusion of women in efficacy studies; 3) requiring analysis of data on sex differences; 4) boosting consideration

a gradual, although existing shift from a disease-centred approach to women's health and related research – merely focusing on disorders associated with the female reproductive system – to a woman-centred approach, which included other burdensome diseases in women's life (e.g. where differences between women and men are more evident in terms of frequency, seriousness, causes or manifestations, treatments or outcomes, morbidity or mortality). This broader concept of woman's health has equally shown variations in the extent of diseases among women from different socio-demographic groups, as well as an uneven distribution of benefits stemming from research developments and novel treatments. Research has also expanded to encompass studies that take into account not only biological sex as a determinant of disease, but also gender, in the sense of emphasizing the importance of social, psychological and behavioural influences. Nevertheless, women representation, consideration and reporting of sex and gender differences in the design and analyses of studies are still inadequate. This hampers advances in women's health research and its translation into clinical practice. The Committee, therefore, recommended mainstreaming women's health research, namely routinely assessing differences between men and women, as well as subgroups of men and women in all health research. It also urged the FDA[19] to enforce compliance with the requirement for sex-stratified analyses of efficacy and safety for medical products (drugs, devices and biologics) that are coming to the market, alongside considering those analyses in regulatory decisions[20].

4. Ethical research conduct

The principle of justice is of paramount importance in conducting an ethical research, especially when recruiting eligible participants to be enrolled in clinical trials. In the context of this article, it may be translated in the researcher's duty to refrain from contributing to inequalities with regard to research designs not adequately taking into account gender-based needs and characteristics in the management of the trial process; or ensuring completeness and accuracy of the information conveyed to research participants, through gender-tailored communication strategies, sensitive to different literacy levels (this is directly linked to guaranteeing free and informed consent). Protecting privacy and confidentiality is another key rule stemming from the principles of respect for the person, and beneficence according to which the latter should be informed about the use of personal data, in order to avoid any harm deriving from the publication of sensitive information. Nevertheless,

of effects of menstrual cycle on drug effect, effects of exogenous hormone therapy on drug effect, and effect of drug on the effects of oral contraceptives, when feasible". See U.S. FOOD AND DRUG ADMINISTRATION (FDA), *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*, 1993.

[19] U.S. GOVERNMENT ACCOUNTABILITY OFFICE, *Women's Health: FDA needs to Ensure More Study of Gender Differences in Prescription Drugs Testing.* HRD-93-17, 1992; U.S. GOVERNMENT ACCOUNTABILITY OFFICE, *Women Sufficiently Represented in New Drug Testing, but FDA Oversight Needs Improvement.* GAO-01-754, 2001; U.S. FOOD AND DRUG ADMINISTRATION (FDA), *FDA Report. Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products*, 2013; U.S. FOOD AND DRUG ADMINISTRATION (FDA), *Collection of Race and Ethnicity Data in Clinical Trials*, 2016.

[20] U.S. INSTITUTE OF MEDICINE, Committee on Women's Health Research, *Women's Health Research: Progress, Pitfalls, and Promise,* cit., p. 13.

the WMA *Declaration of Helsinki*[21] does not specifically refer to women peculiarities in relation to ethical principles for medical research, not even with regard to informed consent. These principles are also included in other crucial international legal instruments in the field of bioethics and research ethics.

In the context of an ethical management of informed consent, it is important to recall that, in 2015, the Committee on Ethics of the American College of Obstetricians and Gynecologists issued the *Opinion n° 646 on Ethical Considerations for Including Women as Research Participants*, in which the responsibilities of researchers were clearly specified, pointing out a set of criteria for an effective disclosure of information in the informed consent process, with a particular emphasis on how to communicate benefits and risks when dealing with pregnant women[22].

5. Rethinking women's specificities in clinical research: from "vulnerability" dimensions to "scientific complexity"

Institutional guidelines are generally keen on not considering women as vulnerable subjects, since this may fuel reticence towards their inclusion in research and hinder the possibility for them of reaping the benefits deriving from participation. However, there are a number of circumstances in which they could be vulnerable in research, such as studies with female sex workers, trafficked women, refugees and asylum seekers; or the case of women who live in a cultural context where they are not permitted to consent on their own behalf for participation in research, but require permission from a spouse or male relative. When women in such situations are potential participants in research, researchers need to exercise special care[23]. Particularly, CIOMS guidelines address major ethical challenges to informed consent deriving from women's conditions of social vulnerability[24]. Caution must

[21] World Medical Association (WMA), *Declaration of Helsinki* (as amended), 2013.

[22] According to the ACOG, "the researcher has an obligation to disclose to women and discuss with her all material risks affecting her; in the case of a pregnant woman, this includes all material risks to the woman and her foetus. Disclosure should include risks that are likely to affect the patient's decision to participate or not to participate in the research. Anything beyond minimal risk must be weighed carefully against the potential benefits to the woman (and the foetus, in the case of a pregnant woman) when the advisability of participation is considered. Because the process of informed consent cannot anticipate all conceivable risks, women who develop unanticipated complications should be instructed to contact the researcher or a representative of the institutional review board immediately". See The American College of Obstetricians and Gynecologists (ACOG), Committee on Ethics*, Ethical Considerations for Including Women as Research Participants. Opinion n. 646*, 2015, p. e102.

[23] Council For International Organizations Of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, Commentary on Guideline n° 15, 2016, p. 58.

[24] The Commentary on Guideline n° 18 stresses the fact that "in many societies women remain socially vulnerable in the conduct of research. For example, they may suffer negligence or harm because of their submission to authority, their hesitancy or inability to ask questions, and a cultural tendency to deny or tolerate pain and suffering. When women in these situations are potential participants in research, researchers, sponsors and ethics committees must take special care in the research design, assessment of risks and benefits, as well as the process of informed consent, to ensure that women have the necessary time and appropriate environment to make decisions based on information provided to them". See Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, Commentary on Guideline n° 18, cit., p. 69.

be used if vulnerable subjects are enrolled in studies; their proposed participation in a research project must always be justified specifically. The general rule is that potential research participants should be the least vulnerable necessary to achieve the goals of the study and appropriate protection should be ensured in these specific cases, in order to guarantee the dignity and safety of women consenting to participate in research[25]. The concept of vulnerability is also mentioned in other international documents, such as in articles 19 and 20 of the *Declaration of Helsinki* (as revised in 2013) and Article 8 of the *UNESCO Universal Declaration on Bioethics and Human Rights* (2005), which calls for both a "negative" duty to refrain from causing harm and a "positive" duty to promote solidarity and to share the benefits of scientific progress, highlighting the close relationship between respect for the integrity and dignity of persons, on one hand, and the vulnerability of persons, on the other, and recognizes special vulnerabilities of women and girls ("gender-related vulnerabilities") concerning treatment in healthcare delivery and research, as they are "particularly exposed to the whole range of social, cultural, economic, educational and political determinants of vulnerability"[26]. Beyond social and cultural patterns leading to vulnerable conditions for women, there are biological reasons: as recalled by the Italian NBC, female subjects' involvement in clinical trials has traditionally been deemed problematic, due to their physiological peculiarities (notably enzymatic and hormonal differences), variations during childbearing and non-childbearing age (i.e. menstrual cycle, pregnancy, breastfeeding, menopause), as well as the possibility of reliance on contraception, in order to avoid pregnancy or for therapeutic reasons; however, estrogens and progestins modify women's metabolism; particularly, estrogens may also interfere with the way genes work. This kind of variability is likely to affect the collection of clear data in mixed sex trials, with an ensuing negative impact on the statistical relevance of the research study. In addition, a possible pregnancy in fertile women is considered another problematic issue for the pharmaceutical industry, as experimental drugs could harm the foetus not only during an unexpected pregnancy while a trial is underway, but also after the end of the process. Therefore, these possible negative effects discourage investments in research involving women, because of the extensive time required for the study development, as well as the rise in insurance costs to cover the emergence of negative consequences. In this regard, CIOMS guidelines point out that "pregnant women must not be considered vulnerable simply because they are pregnant", although recognizing that "specific circumstances, such as risks to the foetus, may require special protections"[27]. This view has been strongly stressed by the Committee on Ethics of The American College of Obstetricians and Gynecologists, which argues that one of the reasons for systematically excluding women from research is their perceived status as "vulnerable", and goes as far as suggesting that "pregnant women in research trials should be defined as 'scientifically complex' rather than a 'vulnerable' population"[28]. This position relies on the fact that vulnerable individuals

[25] Council of Europe, Committee on Bioethics (DH-BIO), *Guide for Research Ethics Committee Members*, 2012, p. 10.

[26] United Nations Educational, Scientific and Cultural Organization (UNESCO), International Bioethics Committee of UNESCO (IBC), *The Principle of Respect for Human Vulnerability and Personal Integrity*, 2013, pp. 5-9.

[27] Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, Commentary on Guideline n° 15, cit., p. 58.

[28] The American College of Obstetricians and Gynecologists (ACOG), Committee on Ethics, *Ethical Considerations for Including Women as Research Participants. Opinion n.646*, cit., p. e102.

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are those with a compromised ability to protect their interests and provide informed consent, whereas pregnant women do not, as a group, fall within this definition. They have the decision-making capacity to opt for participating or not in specific research studies. Nevertheless, pregnant women are a "scientifically complex" group, in the sense that they require tackling a mix of physiological and ethical complexity, which stems from "the need to balance the interests of the pregnant woman and the foetus. Maternal and foetal interests usually align, as appropriate care of the woman is necessary for the health of the foetus, but these interests may diverge in the setting of research, especially when it is not focused on concerns of pregnancy or foetal health"[29]. Moreover, cultural issues and the scientific knowledge gap between researchers and participants, directly affecting the latter's capacity to clearly understand the underlying risks related to their specific health condition should be carefully weighed, especially in these sensitive circumstances. The importance of taking into account the physiological conditions of women is equally highlighted in a set of ICH guidelines[30]. If on one hand classifying women as "vulnerable" in specific contexts should not limit their participation in research and restrict the potential value of findings beneficial for their health; on the other, leaving such a categorization aside must not lead to an under-estimation of risks, protection needs and necessary safeguards peculiar to women's health condition.

5.1. Fertility condition in women

International and European guidelines tend to acknowledge the ethical importance of including women of childbearing potential in clinical studies. It would be unjust to exclude them from clinical studies, since this hampers their chance to reap the benefits of new knowledge obtained from these studies and may result in the impossibility to safely use drugs not tested on women of this group, without adequately protecting the foetus – in case of pregnancy – as they could take drugs available on the market and risk exposure would not be avoided, with potentially dangerous consequences. A number of guidelines place a great emphasis on the self-determination of fertile women in making their own autonomous decision to enrol in clinical studies, as long as they have been duly informed about the specific degree of risk involved in participation. The need to protect the interests and health condition of women often overrides an appropriate consideration of foetus protection measures: according to CIOMS, "access to a pregnancy test, to effective contraceptive methods and to safe abortion must be guaranteed before exposure to a potential teratogenic or mutagenic intervention. The informed consent process must include information about the risk of unintended pregnancy. Moreover, if the pregnancy is not terminated, women must be guaranteed a medical follow-

[29] The American College of Obstetricians and Gynecologists (ACOG), Committee on Ethics, *Ethical Considerations for Including Women as Research Participants. Opinion n.646*, cit.

[30] ICH Guidelines call for "including demographic variables, such as age, sex etc. in research protocols and identifying menstrual status as a possible relevant factor. Where studies are sufficiently large, data should be presented according to these subgroups. At the summary level, the demographic characteristics of patients across all efficacy studies should be provided. Adverse events, extent of exposure and safety-related laboratory measurements and vital signs, etc. should include demographic data such as the age and sex of patients". See International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), *ICH Harmonised Tripartite Guideline. E3*: *Structure and Content of Clinical Study Reports*, 1995.

up for their own health and that of the infant and child"[31]. Nevertheless, as stated in the UK *Guidelines on the practice of ethics committees in medical research with human participants*, "since all contraceptive methods have a very small failure rate, the inclusion of potentially fertile women in pharmacological studies creates a teratogenic risk"[32]. Risk exposure may be high or low; its extent varies according to single studies. Even in the case of women of reproductive age (i.e. not pregnant), the Royal College of Physicians recommends that such risks should be discussed with their partners, also assessing the opportunity to request the latter's consent. It equally encourages researchers to provide appropriate advice concerning contraception precautions and about the existing option of "emergency contraception" if precautions have been omitted. Nevertheless, this possibility is ethically problematic, since it is likely to deter women not willing to run the risk of jeopardizing a potential pregnancy and harming the foetus from participating in high-risk trials, entailing an underrepresentation of specific groups of women. An ethical assessment of the frequency of a health condition in a particular age group also deserves specific consideration, in order to determine whether a study of a disease could be carried out without involving such individuals, because it is rare in this category of women (i.e. old-age diseases). Women who become pregnant during research are removed from the study in cases where a drug or biological product is known to be mutagenic or teratogenic. As a consequence, medical care and follow-up are required throughout their pregnancy, in order to detect and monitor any foetal anomalies. In studies where there is no evidence of a potential harm to the foetus, women who become pregnant are usually not advised to leave the trial, but are given the opportunity to continue or end their participation. Sometimes it may be appropriate for a woman to stay in the study for safety monitoring, despite being removed from the drug study[33]. Other guidelines are more cautious about the inclusion of women of childbearing potential in clinical studies and embrace a balanced approach, which takes into account benefits and risk for both the woman and the foetus: for instance, the Italian NBC emphasized the ethical and social relevance of fertile women participation, "provided that an adequate protection of the unborn child can be guaranteed"[34], alongside recommending a preliminary consultation about the trial, during which clear and accurate information on the goals of the study is provided, as well as a classification of potential benefits and risks that the study may involve for the participant, while highlighting the risks for the foetus in case of pregnancy. Whenever risks for the foetus are envisaged, the NBC underlined the importance of the woman's clear statement of a conscious and responsible commitment to honour abstinence from sexual activity, in order to avoid pregnancy. The NBC also highlighted that the informed consent must be guaranteed, giving women a fair amount of time and appropriate environmental conditions to decide, and that their individual consent cannot be replaced by the partner's consent. Nevertheless, in cases of possible interactions between experimental treatments and the contraceptive methods being used (e.g. certain drug trials can make hormonal contraceptive ineffec-

[31] Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, Commentary on Guideline n° 18, cit., p. 70.
[32] Royal College of Physicians, *Guidelines on the practice of ethics committees in medical research with human participants*, 2007, p. 61.
[33] Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, Commentary on Guideline n° 18, cit., p. 70.
[34] Italian Committee For Bioethics (NBC), *Opinion on Pharmacological trials on women*, cit., p. 18.

tive), the NBC recommends that the woman (and her partner) receive adequate information; recruitment should follow only if a commitment is clearly expressed in the informed consent "to avoid starting a pregnancy during the time of the trial and, in some cases, also for a certain time afterwards, a time to be defined according to the typology of the trials. The woman, on her part, must be available to carry out checks (pregnancy tests) that allow the experimenters to verify the conditions of safety to proceed"[35].

A necessary reliance on contraception to avoid pregnancy, as a requirement for participation in clinical research, can become ethically problematic especially when such prescriptive contraceptive methods clash with moral and religious beliefs, resulting in a possible barrier to research enrolment decision-making.

The use of contraception is a highly controversial and ethically sensitive issue in the Italian debate, as in many cases where fertile women are involved research sponsors consider it a mandatory requirement for participation. Despite the existence of a variety of stances on this topic, which reflects an ethical pluralism in our current society, it is possible to identify two main positions that oppose this mandatory requirement: a first one upheld by those who criticize the expectation of the pharmaceutical industry that women should use hormonal contraceptives, as this requirement would restrict women's freedom, intended as self-determination (e.g. the possibility to choose among different options); others also argue that relying on hormonal contraceptives as a mandatory requirement is not morally acceptable, since it would be detrimental to the freedom and responsibility of research participants, but inspired by a different perspective. This position, supported by those who believe in the inseparability of the unitive and procreative dimensions of the marital act, claims that the woman's explicit commitment to avoid pregnancy is sufficient, and that she should be able to choose birth control methods, respectful of her lifestyle and values, including abstaining from sexual intercourse[36]. The NBC's balanced approach aimed at protecting both the woman and the foetus is also upheld by the Austrian Bioethics Commission, which stressed that clinical trials on fertile women should be conducted in ways that avoid posing risks to the unborn child, while recommending the formulation of rules for a woman-friendly study design of research projects[37].

5.2. Safety of clinical research with women: before, during and after pregnancy

Both at the international and European levels, particular consideration is devoted to the significance of clinical research involving pregnant women, insofar as it improves knowledge of conditions and treatments of diseases related to pregnancy. These diseases may affect the woman, the foetus or both.

In this context, CIOMS highlighted the fact that a systematic exclusion of pregnant and breastfeeding women from clinical research leads them to take prescription/non-prescription drugs, which often lack sufficient safety and efficacy evidence, with ensuing potentially high maternal, fetal or neonatal

[35] ITALIAN COMMITTEE FOR BIOETHICS (NBC), *Opinion on Pharmacological trials on women*, cit., p. 19.
[36] ITALIAN COMMITTEE FOR BIOETHICS (NBC), *Opinion on Pharmacological trials on women*, cit., pp. 12-13.
[37] AUSTRIAN BIOETHICS COMMISSION, *Recommendations with Gender Reference for Ethics Committees and Clinical Studies*, cit.

risks[38]. As recalled by the Committee on Bioethics of the Council of Europe in the *Guide for Research Ethics Committees*, research conducted on pregnant women may or may not have a potential direct benefit and is allowed only when studies of comparable effectiveness cannot be carried out on other persons; for research with potential direct benefit, the risk-benefit assessment must consider the specific situation of pregnancy, whereas research without potential direct benefit "must contribute to the ultimate attainment of results capable of conferring benefit to other women in relation to reproduction or to other foetuses. However, in such research the criteria of minimal risk and minimum burden are compulsory"[39] In addition, if involving breastfeeding women, particular care is recommended to avoid any adverse impact on the health of the child. The issue of "minimal risk" was particularly raised in the US ethical debate in relation to the definition provided in federal regulations (according to which, the likelihood and degree of harm or discomfort anticipated in the research, should not be greater than those experienced in daily life or during the performance of routine physical or psychological examinations). It was unclear whether "daily life" referred to that of the general population or of individual participants. Relying on the participant's daily life as the standard might make a higher level of risk acceptable; hence, the general population standard is advised[40]. Although, CIOMS underlined that "when the social value of the research for pregnant or breastfeeding women or their foetus or infant is compelling, and the research cannot be conducted in non-pregnant or non-breastfeeding women, a research ethics committee may permit a minor increase above minimal risk"[41]. This last aspect requires research ethics committees to act with particular caution: the safety of persons who consent to research must always be the primary concern of research ethics committees and researchers; as a general rule, this implies that all risks be carefully weighed against expected benefits. In any case, relying on evidence from prior animal experimentation is absolutely necessary[42].

[38] The Commentary on Guideline n° 19 specifies that "physicians prescribe medications for pregnant and breastfeeding women, but most often do so in the absence of studies involving such women and without adequate evidence of safety and efficacy. Such routine treatment includes medications that may have a prospect of serious harm to the foetus, such as radiation or chemotherapy for cancer. A direct consequence of the routine exclusion of pregnant women from clinical trials is their use of medications (both prescription and non-prescription) lacking data from clinical trials about the potential individual benefits and harms to themselves, their foetuses and their future children. Therefore, after careful consideration of the best available relevant data, it is imperative to design research for pregnant and breastfeeding women to learn about the currently unknown risks and potential individual benefits to them, as well as to the foetus or nursing infant". See COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, Commentary on Guideline n° 19, cit., p. 72.

[39] COUNCIL OF EUROPE, COMMITTEE ON BIOETHICS (DH-BIO), *Guide for Research Ethics Committee Members*, cit., p. 46.

[40] THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG), Committee on Ethics, *Ethical Considerations for Including Women as Research Participants. Opinion n. 646*, cit.; U.S. NATIONAL BIOETHICS ADVISORY COMMISSION, *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries, Report and Recommendations*, Bethesda, Maryland, vol. I., 2001.

[41] COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, Guideline n° 19, cit., p. 71.

[42] THE FRENCH NATIONAL CONSULTATIVE ETHICS COMMITTEE FOR HEALTH AND LIFE SCIENCES (CCNE), *Cooperation in the field of biomedical research between French teams and teams from economically developing countries. Report*, 1993.

The Royal College of Physicians identified a number of specific criteria for pregnant/breastfeeding women inclusion in research, in an attempt to balance the requirements of protecting the safety and health of both the mother and the foetus or infant with potential benefits stemming from research advancements[43].

In this regard, the Committee on Ethics of the American College of Obstetricians and Gynecologists dealt with the type of information to be provided in case of pregnancy exposure to more than minimal risk in the course of a study[44]. In the context of safety concerns before enrolling in clinical trials on investigational medicinal products, the European Clinical Trial Facilitation Group (CTFG) issued recommendations related to embryo-foetal risk mitigation and risk assessment during preconception and early stages of pregnancy[45]. The CTFG stressed the need to clearly provide in the trial protocol the analysis of embryofetal risk for clinical trials with investigational medicinal products (IMPs), including recommendations for the level of contraception and frequency of pregnancy testing, as well as detailed information on the possibility for interaction between the investigational medicinal product or non-investigational ones and hormonal contraceptives, since this may reduce the efficacy of the contraception method. However, as emphasized by the Committee on Ethics of the American College of Obstetricians and Gynecologists, "concerns about the potential for pregnancy in research trial participants have led to practices involving overly burdensome contraception requirements (such as the use of intrauterine devices or bilateral tubal occlusion), which are out of proportion to the actual risks of experimental drugs or interventions"[46]. Therefore, it advises consultation with an obstetrician-gynecologist or other gynecologic care provider regarding the efficacy and risk of contraception measures, since investigators generally fail to consider what is actually "reliable": the required methods, which are often prescriptive and potentially coercive, have their own inherent risks and may not meet the woman's preference. Highly burdensome contraception could be inappropriate based on the principles of respect for autonomy, beneficence and justice. In this sense, a woman should be allowed to choose a birth control method, including abstinence, according to her needs

[43] According to the Royal College of Physicians, "pregnant or breastfeeding women should not participate in non-therapeutic research that carries more than minimal risk to the foetus or infant, unless this is intended to elucidate problems of pregnancy or lactation; while, as a general rule, therapeutic research should only be undertaken in pregnant or breastfeeding women with a view to: 1) improving the health of the mother without prejudice to that of the foetus or breast-fed baby; or 2) enhancing the viability of the foetus; or 3) aiding the baby's healthy development; or 3) improving the ability of the mother to nourish it adequately". See ROYAL COLLEGE OF PHYSICIANS, *Guidelines on the practice of ethics committees in medical research with human participants*, cit., p. 62.

[44] The Committee on Ethics of the American College of Obstetricians and Gynecologists points out that "pregnant women who enrol in a research trial and experience a research related injury should be informed about their therapeutic options, including those related to the pregnancy. When a pregnancy has been exposed to more than minimal risk in the conduct of research, the woman should be encouraged to participate in any available follow-up evaluations to assess the effect on her and her foetus or child". See THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG), Committee on Ethics, *Ethical Considerations for Including Women as Research Participants. Opinion n. 646*, cit.

[45] CLINICAL TRIAL FACILITATION GROUP (CTFG), *Recommendations related to contraception and pregnancy testing in clinical trials*, 2014.

[46] THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG), Committee on Ethics, *Ethical Considerations for Including Women as Research Participants. Opinion n. 646*, cit., p. e100.

and values. In addition, in the Committee's view, "requiring specific contraception in a woman not sexually active violates a commitment to respect her as a person"[47]. This ethical position is in line with the concerns raised by the Italian Committee for Bioethics. As part of the consent process, the woman should be duly informed of all types of risks (including those risks impacting on her decision to enrol or not enrol in research), that could be affecting her and/or her foetus in case of pregnancy. If new scientific information arises during the research, this information should be conveyed to participants as soon as possible. In this case, the CoE Committee on Bioethics (DH-BIO) recommends that participants be told whether the research ethics committee has asked researchers to prepare revised information/new consent forms regarding modifications to the project. At this point, as at any stage in the course of the research, subjects' right to withdraw consent must be respected[48]. For clinical trials including pregnant women because the medicinal product is intended for use during pregnancy, follow-up of the pregnancy, foetus and child is essential, even for several months after the end of the study. If experimentation is carried out on breastfeeding women, "excretion of the drug or its metabolites into human milk should be examined, where applicable; in this case, their babies should also be monitored for the effects of the drug"[49].

5.3. Maternal and foetal health in pregnancy: balancing benefits and risks

As discussed earlier, conducting clinical trials on pregnant women is an ethically problematic issue, since maternal and foetal risks are deeply interconnected and the decision to enrol this category of women in research presupposes balancing the possible risk of foetal harm with the potential for benefit and the importance of the information to be gained on the health of women and foetuses[50]. Particularly, it may be highly problematic to decide whether to enrol in research directed at benefiting the mother in which the possibility of foetal loss cannot be excluded; in this case, it is a matter of weighing maternal welfare against foetal risk, as for studies of epilepsy or psychosis in pregnancy[51]. In this context, it is noteworthy mentioning the controversial bioethical debate surrounding the status of the foetus, recalled by the NBC: some argue that when balancing the possible damage to the foetus (considered not yet to have dignity "in the strong sense") with the potential direct benefits to women, primary consideration should be given to the latter, since an *a priori* exclusion of women to protect the foetus would result in injustice in research, given that women would not have the same opportunities as men in the treatment of certain diseases; others argue that where clinical research is likely to jeopardize the foetus's life and health (according to this stance, the foetus is recognised as a subject having dignity "in the strong sense"), even only hypothetically or potentially, it is ethically advisable for these women not to participate in trials, since the risk to the new life overrides the po-

[47] The American College of obstetrIcians and Gynecologists (ACOG), Committee on Ethics, *Ethical Considerations for Including Women as Research Participants. Opinion n. 646*, cit., p. e103.
[48] Council of Europe, Committee on Bioethics (DH-BIO), *Guide for Research Ethics Committee Members*, cit.
[49] European Medicines Agency (EMA), *Note for Guidance on General Considerations for Clinical Trials*, cit., p. 10.
[50] The American College of Obstetricians and Gynecologists (ACOG), Committee on Ethics, *Ethical Considerations for Including Women as Research Participants. Opinion n. 646*, cit., p. e101.
[51] Royal College of Physicians, *Guidelines on the practice of ethics committees in medical research with human participants*, cit., p. 63.

tential benefits to the women[52]. The accuracy and clarity of the information provided in these sensitive contexts is key to ensuring the prospective participants' full understanding of the potential benefits and the extent of risk at stake.

When dealing with pregnant women, another ethically sensitive issue concerns foetal protection within disease prevention research: investigation into pathological conditions (such as toxoplasmosis, deformities, etc.) or treatments specifically aimed at the foetus may equally be the focus of research studies. The primary goals of these interventions is to improve the health of children by intervening before birth to correct or treat prenatally diagnosed abnormalities. However, since this leads to unavoidable consequences for the woman's health and bodily integrity, it cannot be carried out without consideration of her wellbeing and without her explicit consent[53].

5.4. The impact of socio-economic conditions on freedom and self-determination

Social and economic vulnerabilities may interfere with the self-determination of individuals and lead to a remarkably increased exposure to a number of risks: some contextual aspects that fuel social vulnerability in research concern poverty and low educational levels, difficulty in accessing healthcare (i.e. whenever transnational research projects are involved), as well as the interaction between gender and marginalised racial and ethnic backgrounds[54]. In this regard, the French National Consultative Ethics Committee for Health and Life Sciences (CCNE) highlighted the special status of women in some developing countries, that generates "a situation of inequality in the gender relationship", which deserves particular attention, since it could compromise an actual understanding of health issues[55]. Respect for free and informed consent acknowledges that potential research participants must not be coerced or unduly influenced by use of inducements (both direct or indirect) or threats. For instance, the IBC discussed cases of poor women in developing countries deciding to enrol in trials after being informed that their children would be entitled to receive necessary medical treatments in this context. Therefore, these women's ability to provide a valid consent was in doubt, given their concern for their children's health. In addition, they become vulnerable to any risks involved in clinical trials, since they are likely to underestimate these aspects due to other priority interests. As recalled by the CoE Committee on Bioethics (DH-BIO), "it is extremely difficult to achieve a complete lack of influence, but influence that would lead individuals to accept a higher level of risk than would otherwise be acceptable to them, would be considered undue. This kind of influence may be financial in nature, but could also include, for instance, attempts to influence family members" (as in the case of vulnerable women accustomed to social conditioning to submit to authority), or veiled

[52] Italian Committee for Bioethics (NBC), *Opinion on Pharmacological trials on women*, cit., pp. 12-13.

[53] The ACOG made clear that "it is impossible to enrol the foetus in a clinical study without affecting the pregnant woman either physically (i.e. in the case of surgical treatments) or pharmacologically (as when drugs given to women cross the placenta to treat the foetus)". See The American College of Obstetricians and Gynecologists (ACOG), Committee on Ethics, *Ethical Considerations for Including Women as Research Participants. Opinion n. 646*, cit., p. e105.

[54] United Nations Educational, Scientific and Cultural Organization (UNESCO), International Bioethics Committee of UNESCO (IBC), *The Principle of Respect for Human Vulnerability and Personal Integrity*, cit., p. 27.

[55] The French National Consultative Ethics Committee for Health and Life Sciences (CCNE), *Disparity in access to health care and participation in research on a global level-ethical issues. Opinion n°78*, 2003, p. 19.

threats (for example by researchers, medical staff or healthcare providers) to deny access to services to which individuals would otherwise be entitled, or expectation of any other retaliatory response from senior members of a group with a hierarchical structure in case of refusal to participate in a trial. Therefore, special care is needed in situations where participation in a research project may be the only way to access health care[56]. The CoE Committee on Bioethics (DH-BIO) does not refer to gender issues in this specific context. In principle, the involvement in a clinical trial is a benevolent act, which should not be induced by monetary or other forms of compensation, in order to avoid exploitation[57]. Although, it is considered ethically acceptable and appropriate to reimburse individuals for any costs associated with participation in research, including transportation or lost wages. A number of research ethics committees also believe that participants should receive compensation for their time devoted to research participation; however, WHO recommends that payments should not be so large, or free medical care or other forms of compensations so extensive, as to provide prospective participants with incentives to consent to research enrolment against their better judgment or to undermine their understanding of the research[58]. However, determining the ethical acceptability of compensation is problematic, as the possibility it may exert an undue inducement to participate in research depends on a number of different variables, such as prospective subjects' economic status. An ethical consideration of informed consent must focus on comprehension and free consent, as both elements are an essential part of the person's self-determination: it is all the more important when dealing with vulnerable categories of women that potential participants are given clear information in language, which is understandable to them, particularly when subjects with linguistic or cognitive limitations are involved. This is a necessary aspect for freedom in consenting. In addition, the Committee on Ethics of the American College of Obstetricians and Gynecologists advises those in charge of providing information "to be cognizant of participants' beliefs and values during the informed consent process"[59].

6. A gender approach to informed consent

In the context of informed consent, the issue regarding comprehension of information conveyed by investigators or practitioners is often raised in developed countries where illiteracy can be a minor problem, but where inability to understand is due to the complexity and length of documents submitted to research participants (however, also in clinical practice). More than empowering subjects through clear information, these documents may be interpreted as a way to protect healthcare professionals from being accused of delivering incomplete information. The International Bioethics Committee (IBC) of UNESCO, therefore, recalls the importance of the clarity of the text submitted and its content, which should include necessary and sufficient information to decide either to con-

[56] Council of Europe, Committee on Bioethics (DH-BIO), *Guide for Research Ethics Committee Members*, cit., 10.
[57] European Group on Ethics in Science and New Technologies (EGE), *Ethical aspects of clinical research in developing countries*, 2003, p. 13.
[58] World Health Organization (WHO) Department of Ethics, Equity, Trade and Human Rights, *Standards and operational guidance for ethics review of health-related research with human participants*, cit., p. 14.
[59] The American College of Obstetricians and Gynecologists (ACOG), Committee on Ethics, *Informed Consent. Opinion n°439*, 2009, p. 3.

sent or refuse to consent. This must be done in a language that is accessible to person concerned. Other ethical challenges stem from the fact that in many cases, particularly in scientific research, it may be necessary to document in a written form that consent has been obtained. However, the implementation of this request is likely to face problems, in certain situations: for instance, in societies with an oral tradition, where the value of oral consent is unquestionable; as a consequence, written form consents can be considered as a lack of trust or even as an insult; or in illiterate groups of people, "where a sign at the bottom of a page may not reflect a real agreement with the content of the document"[60]. Hence, there is wide recognition that, in principle, despite the need of an assiduous effort towards the possibility of obtaining written consent, based on the context, it is appropriate to explore other ways of demonstrating that consent has been actually and consciously expressed. Nevertheless, the IBC does not specifically apply literacy issues to gender considerations. In this context, the German Working Party of research ethics committees[61] has developed and published samples for informed consent, which are documents for clinical trials with medicinal products on healthy volunteers or patients and for collecting materials for biobanking, recommended to sponsors. Even though they are not adapted to gender, these documents stress that the oral information process must take account of the background and abilities of the person concerned.

In Canada, a set of initiatives have been carried out to provide guidance on women enrolment in clinical research by issuing a number of documents in this area, which are particularly interesting for their major focus on tailoring the informed consent process to female peculiarities in terms of communication skills: particularly, in 2006, the Canadian Working group on Women and Health Protection published a document on *The Inclusion of Women in Clinical Trials: Are We Asking the Right Questions?*, placing a strong emphasis on the need to adapt consent forms to women's specificities and literacy levels and overcoming the "pro-forma" model[62].

The Working Group therefore recommended that efforts be made to ensure consent forms are "userfriendly", without leaving out important informational content in order to be able to give an actual consent, well aware of the potential benefits and risks related to enrolment. In addition, Canadian guidelines raise awareness about the possibility of gender-based differences in how the informed consent process is carried out, due to potential gender and class-based diversities in doctor-patient relationships. These guidelines equally stress the importance of making "reader-friendly" summaries of trial protocols easily available and envisaging the development and use of multiple means of communication (i.e. Internet, print, oral, multiple languages, etc.), to ensure all women can have ac-

[60] United Nations Educational, Scientific and Cultural Organization (UNESCO) IBC, *Report On Consent*, 2008, p. 35.

[61] Working Party of Research Ethics Committees in Germany, *Merkblatt zur Verwendung der Mustertexte für die Patienten-/Probanden-information und – einwilligung empfohlen vom Arbeitskreis Medizinischer Ethik-Kommissionen gemäß Beschluss*, 2008.

[62] The Canadian Working Group on Women and Health Protection clarified that "this requires attention both to informed consent material, and the informed consent process. Given literacy levels of women and the complexity of forms, there are concerns about women expressing truly authentic consent to trial participation. And even with women who are print literate, other factors related to expectations of medical care, understanding of random assignment, placebos, and of probability, can compromise the ability to give truly informed consent". See Canadian Working Group on Women and Health Protection, *The Inclusion of Women in Clinical Trials: Are We Asking the Right Questions?*, 2006, p. 26.

cess to complete and accurate information, combined with related materials[63]. All these tools are meant to guarantee full understanding of the research process with a gender perspective. Institutional documents particularly underline a number of key elements pertaining to the consent process, whenever enrolling women of childbearing potential: in this case, clinical trial participants should be duly informed, alongside all other risks, about the potential risks of reproductive and foetal toxicity, including teratogenicity and about pregnancy prevention, so that prospective subjects understand how and when to take precautions (i.e. use of reliable methods of contraception and/or abstinence, pregnancy testing) to prevent pregnancy, if necessary within the trial. Moreover, Health Canada recommends that a statement on the effectiveness of contraception methods should be included in all informed consent forms requiring contraceptive guidance, as well as a clear list of the contraceptive methods suggested. Whenever relevant information is not available from reproductive toxicity studies, the informed consent form should explicitly note that embryo-foetal risk cannot be excluded[64].

7. Sensitive issues related to the acquisition of informed consent

7.1. The role of the pregnant woman's partner in the informed consent process

Clinical studies involving female or male reproductive health may raise issues surrounding the potential effect of the study on the participant's partner. According to the ACOG Committee on Ethics, "in the absence of a few specific scenarios, requiring participation consent from a woman's partner is neither warranted nor ethically justified"[65] (for instance, in cases of general medical care or whenever pregnancy decisions are involved). It is deemed appropriate if there is a risk of the partner's exposure to an investigational agent and this is likely to carry more than a minimal risk or if data regarding him will be collected; or if testing of a partner is required for a woman to participate in a study (eg. semen analysis or testing for a sexually transmitted infection). Beyond these circumstances, the consent of the woman's partner in not advisable, since it may hinder the woman's decision with regard to health issues.

Conversely, a more balanced position is expressed by CIOMS: even if it firmly states that a partner can never replace the consent of the woman, whenever the latter expresses willingness to seek her partner's advice before making a decision with regard to potential participation in research, this possibility should be granted[66].

[63] Canadian Working Group on Women and Health Protection, *The Inclusion of Women in Clinical Trials: Are We Asking the Right Questions?*, cit., pp. 26-27.

[64] Health Canada, *Guidance Document: Considerations for Inclusion of Women in Clinical Trials and Analysis of Sex Differences*, 2013, p. 5.

[65] The American College of Obstetricians and Gynecologists (ACOG), Committee on Ethics, *Ethical Considerations for Including Women as Research Participants. Opinion n. 646*, cit., p. e103.

[66] Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, Guideline n° 19, cit., p. 72.

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7.2. An ethical reflection on pregnancy/breastfeeding and the role of the man's pregnant partner or of childbearing potential in the informed consent process

The Belgian Advisory Committee on Bioethics has dealt twice with the topic of pregnant women's participation in research: in 2004, it issued a first *Opinion regarding experiments on pregnant and breastfeeding women*[67] and, in 2015, a second one on *The Ethical implications of the "Statute" of the Pregnant Partner of a Male Participant in a Clinical Trial*[68], in which it provided a detailed description of key ethical and legal issues related to the informed consent process in the context of pregnancy. In its *Opinion n° 31 regarding experiments on pregnant and breastfeeding women*, the Belgian Advisory Committee on Bioethics, noted that research ethics committees should take into account the various stages of pregnancy that are linked with a totally different set of risks (i.e. possible effects on germ cells or the implantation of fertilized eggs cells, potential teratogenic effects, possible embryotoxic effects and the impact on the physiological changes caused by pregnancy) when assessing protocols for experiments on pregnant women. Hence, in terms of safety, an appropriate analysis of the many underlying issues should differentiate the different stages involved in the process: before conception; the first week of the pregnancy; the second week up to and including the eighth week; the second and third trimesters and the delivery. Research involving pregnant women may be conducted for different reasons, which raise a number of specific ethical issues, ranging from research into problems specific to pregnancy (i.e. pregnancy-related pathological complications such as repeated miscarriages) to physiological or physiopathological research (for instance, concerning circulatory changes during pregnancy). In this case, both the mother and the child may benefit from the study and its results, since they are relevant to the goals of the research. In other cases, trials can be carried out to look into pathological conditions that are not linked to pregnancy, but that occur in pregnant women and, therefore, result in diagnostic or therapeutic problems (for instance, the diagnosis or treatment of hyperthyroidosis). Here, concern is mostly for any adverse effects on the unborn child that could be caused by the drug used; whereas, the benefits to the foetus are generally less important. The Belgian Committee equally recalled different types of research directed at benefitting the foetus (i.e. pathological conditions generally affecting the foetus). These studies may also include investigations into the extent to which treatment can protect mother-to-child transmission of HIV virus[69].

In the context of interactions between gender and multicultural issues, emphasis was placed on the fact that an over-representation of women belonging to socially disadvantaged or minority groups should be avoided, as their decision to enrol in a trial may be influenced by receiving free medical care. Likewise, they should not be systematically excluded either; nevertheless, it is important to make sure they actually have fully understood the consent form presented to them[70].

[67] BELGIAN ADVISORY COMMITTEE ON BIOETHICS, *Opinion n° 31 of 5 July 2004 regarding experiments on pregnant and breastfeeding women*, 2004.

[68] BELGIAN ADVISORY COMMITTEE ON BIOETHICS, *Opinion n° 62 of 12 October 2015 on the Ethical Implications of the "Statute" of the Pregnant Partner of a Male Participant in a Clinical Trial*, 2015.

[69] BELGIAN ADVISORY COMMITTEE ON BIOETHICS, *Opinion n° 31 of 5 July 2004 regarding experiments on pregnant and breastfeeding women*, cit., p. 2.

[70] BELGIAN ADVISORY COMMITTEE ON BIOETHICS, *Opinion n° 31 of 5 July 2004 regarding experiments on pregnant and breastfeeding women*, cit., p. 5.

Moreover, considerable attention has been focused on the role of the man's fertile or pregnant partner in the consent process. This issue arises from the fact that some drugs being tested in clinical trials are potentially toxic for gametes or foetuses, resulting in possible consequences for any offspring conceived during the study. The Belgian Committee addressed this topic in the context of toxicity caused by the sperm of a male participant or when toxicity affects the gametes of a male participant. Its focus was on whether it would be necessary to request the pregnant partner's consent prior to research participation. Because of the sensitiveness of this issue, the Committee underlined the importance of a thorough and adequate informed consent process, with the duty to inform the male participant in a complete, clear and understandable manner regarding the potential medical risk of the test product for both the participant himself and his partner. In this perspective, it is primarily the responsibility of the sponsor to limit the risks related to the study to a minimum. In addition, a number of specific recommendations are made on the informed consent process[71]. However, no compulsory requirement to obtain the consent of the male participant's fertile or pregnant partner is suggested. The Italian NBC does not specifically address the issue of acquiring consent from a male participant's partner, but equally recommends that the informed consent and commitment to avoid procreation should apply to men participating in a clinical trial, which carries a risk of harm to the foetus through their gametes[72].

8. Conclusions

In order to improve the informed consent process with a gender perspective, it is important to envisage a set of ethical standards focusing on women's specificities in clinical research, which could contribute to overcoming current ethical challenges, that were discussed in this paper in relation to their inclusion: first, possible interactions between changes in women's physiological conditions and the use of experimental pharmaceuticals should be clearly conveyed in the informed consent process, with regard to the implications related to the fertility condition and the possible pregnancy and possible damages to the embryos and foetuses. The informed consent must highlight benefits and any possible risks (specifying the extent, envisaged or potential) for embryos and foetuses in case of pregnancy. Second, a fertile woman should be aware and fully informed of methods to avoid pregnancy before, during and after the trial (the period of risk is to be defined and communicated according to the type of trial). This information should be clearly provided by the researcher, respecting the woman's choices and moral or religious convictions. Communicating contraception requirements should also include referring to any inherent risks related to its use.

[71] According to the Belgian Advisory Committee on Bioethics, the informed consent process should include: "1) the period of risk exposure; 2) that the pregnancy of the partner or a refusal to use double contraception are considered to be exclusion criteria; 3) that the participant is encouraged to inform his partner about his participation in a clinical trial; and that the sponsor of the clinical trial formally declares to be prepared to answer the questions of the participant's partner". See BELGIAN ADVISORY COMMITTEE ON BIOETHICS, *Opinion n° 62 of 12 October 2015 on the Ethical Implications of the "Statute" of the Pregnant Partner of a Male Participant in a Clinical Trial*, cit., p. 10.

[72] ITALIAN COMMITTEE FOR BIOETHICS (NBC), *Opinion on Pharmacological trials on women*, cit., p. 19.

Indeed, the woman should be given a fair amount of time and appropriate environmental conditions to make her free and informed decision and be aware of the possibility for her to revoke consent, at any time, during research, as well as informed of any envisaged risks also after experimentation.

Third, definitions of minimum risk and burden or above this minimum threshold should be provided in the context of clinical research, especially when dealing with fertile, pregnant or breastfeeding women. This information should be clearly explained and communicated before any decision to participate is made.

Fourth, for clinical trials including pregnant women, follow-up of the pregnancy, foetus and child is essential, even for several months after the end of the study. This safety requirement should be clearly communicated during the informed consent process.

If research is carried out on breastfeeding women, participants should be adequately informed of the need to monitor the possible excretion of the drug into human milk, as well as their babies for the effects of the drug. Fifth, pregnant or breastfeeding women should be encouraged to involve their partners in the informed consent process. The degree of involvement of partners may be adapted to participation risks and requires the elaboration of adequate criteria, which need to be explicitly mentioned before experimentation.

Equally, men participating in research which is potentially toxic for gametes or foetuses should not only receive clear and detailed information on the risks linked to their enrolment, but also be requested to involve their fertile or pregnant partners in the consent process. Criteria for their involvement should also be defined.

Sixth, researchers must make sure that women from vulnerable social contexts, and with low literacy levels, have fully understood all benefits and risks related to clinical research enrolment and freely consented to participate. They should devise adequate tools to verify appropriate comprehension levels of what is at stake through a participant-tailored approach to communication.

Caution is especially needed whenever low-income women are enrolled in research, in order to make sure they have not been coerced (through social conditioning or pressures by medical staff or research team) or unduly influenced (financially or offering better healthcare) to participate, in ways that would lead these women to accept a higher level of risk than would otherwise be acceptable to them. It is of paramount importance to verify that there is no underestimation of such aspects due to other priority interests.

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Special issue

Interreligious and Cross-Cultural Perspectives on Informed Consent in the Light of Human Rights and Mental Privacy

Alberto García Gómez, Mirko Daniel Garasic*

ABSTRACT: Even if under a lot of stress at the moment, human rights are generally considered to be absolutes that should not be touched nor put into question. Yet, recent biotechnological and neuroscientific discoveries have led many scholars to call for an increase in the level of alert that such changes in our society could imply -reaching the suggestion that we should implement new, additional human rights (cognitive liberty, mental privacy, mental integrity, psychological continuity) aimed at dealing with the specific threats that our mental privacy, autonomy and integrity could suffer from. Surely this scenario includes in direct ways our approach to informed consent and the objective of this paper is to highlight how six of the most prominent religious traditions and cultures in the world (Buddhism, Christianity, Confucianism, Hinduism, Islam and Judaism) can interact with these new human rights, underlining the specific role of informed consent within each tradition and in which way the possible implementation of this new way of conceptualizing human rights could impact -if at all- on any of the already established guidelines of each of them.

KEYWORDS: Autonomy; human rights; informed consent; neuroethics; religion

SUMMARY: 1. Introduction – 2. Neuroscience and Human Rights – 3. Biolaw and Human Rights – 4. The Principle of Responsibility, Human Rights and Neuroethics – 5. New Human Rights: How Would Those Affect Informed Consent? – 6. New Human Rights, Informed Consent and Religion – 7. Conclusions.

1. Introduction

«That there are similar bioethical problems in different countries does not imply that the same ethical approach exists everywhere. The global dimension, however, invites us to rethink our usual approaches and ethical frameworks. It makes us aware of the "locality" of our own moral views while, at the same time, encouraging us to search for moral views that are shared globally. In this challenge, bioethics is increasingly connected with international law, particularly human rights law, which has a similar global vision[1]".

* *Alberto García Gómez: Professor – UNESCO Chair in Bioethics and Human Rights. E-mail: agarcia@unescobiochair.org; Mirko Daniel Garasic: Research Scholar – UNESCO Chair in Bioethics and Human Rights. E-mail: mgarasic@unescobiochair.org.* *The article was subject to a double-blind peer review process.*
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Rapid developments and discoveries in biotechnology and neuroscience challenge us with new, at times unpredictable, moral dilemmas that have great scope and impact. Surely, the global interconnectedness of our times pushes us more than ever to enquire and discuss said challenges in an inter-religious and cross-cultural perspective because we believe that such an exchange of views has, in itself, an added value for the progress of human dialogue. Here, our focus will be on drawing a map of the relationship between human rights and global bioethics, and then move towards the specific problem that some new human rights invoked in the field of neuroethics could represent for society. Lastly, we will highlight how such new human rights would interact with six of the most prominent religious traditions in the world, hoping to contribute to the fostering of dialogue among different groups of people in the world and increasing the exchange of knowledge in relation to rapid neuro-ethical challenges we are facing as a global community. Hence, to begin with, let us look into the relationship between human rights and neuroscience.

2. Neuroscience and Human Rights

When considering the relationship between neuroscience and human rights, it is important to clarify what we understand by human rights. They are the set of goods whose recognition, protection and guarantee, in each historical moment, specify the requirements of dignity, freedom and equality, which must be positively recognized by legal systems, at both national and international level.

When we say that they are "goods" we mean that they are "valuable things", that is, realities that human beings are endowed with that are objectively essential and fundamental for our existence and for our development. The classic definition of justice as "giving each one his own" helps us to understand this concept a bit abstract, but no less real. "What is yours" is "what belongs to each one". The very nature of human rights characterizes them as universal, since all human beings possess them by default when coming into existence. This is one of the reasons why we define human rights as inherent, that is, inseparable from the human condition. They arise with the new human being and are extinguished with the death of the person. Precisely because they are essential goods and endowed with an objective value, human rights are not susceptible to acts of domination. This assumes that such goods are so fundamental to our existence and development like people who cannot be bought or sold, given away or renounced. Not even the individual can renounce them, nor, of course, can the State arrogate to itself the right to dispose of them legitimately, invoking the benefit of the community. In this sense, we say that human rights are unconditional, because they should not be violated, infringed or arbitrarily limited.

From this general understanding of human rights, we can better understand the extent to which neuroscience and its applications, in the form of neurotechnology, can contribute to the satisfaction or realization of these rights -as well as creating space for further integrations on the list we currently have drafted as a document with the Universal Declaration of Human Rights (UDHR)[2]. The creation (or acknowledgment) of such rights entails correlative human duties. Indeed, there are no real and

[1] H. TEN HAVE, *Respect for Cultural Diversity and Pluralism*, in P. J. THAM; K. KWAN; A. GARCIA (eds.), *Religious Perspectives on Bioethics and Human Rights*, Cham, Switzerland, 2017, p. 10.

[2] www.un.org/en/universal-declaration-human-rights/index.html (last visited 14/06/2019).

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effective rights if each right that is invoked as such (in a strong sense) is not associated with a correlative duty (or responsibility to do or not do) on the part of another person, group of people or an institution.

Human rights, therefore, have an ethical groundwork, since they are presented as a set of objective moral demands -they do not depend on consensus or the parliamentary majorities that approve and promulgate positive laws. In other words, my life, my freedom and my dignity do not depend on an authority or a law to recognize them. They are goods (valuable things in themselves) that belong to me because of the simple fact that I am a human being. Therefore, human rights are prior to positive law. However, human rights so conceived have a legal vocation - they must be positivized. Hence, the State (the legitimate authority of a certain political community) has the task and duty to recognize them, to guarantee them and to promote them as a way to facilitate and promote peace, social cohesion and mutual coexistence. The State, therefore, does not create human rights - as these belong to every human being - but it has a duty to recognize and protect these rights so that, such a positive law (democratically approved in a parliament) that does not recognize or ignore such rights must be considered an unjust law.

From a religious perspective, the brain, mind and spirit are fundamental assets of the person. These three realities can only be understood in their inherent relationship and always forming part of the totality of the person which is a human body, in the sense that it is not an organism like any other (an object according to the legal categories), but belongs to the higher existential and ontological order that constitutes him/her as a subject, naturally endowed with a special value, which we call human dignity, and a unique social-relational capacity, which distinguishes and differentiates animate and inanimate beings. The complexity of the interactions and correlations between the body, the brain, the mind and -within a religious scheme- the soul has led to conceptualization as a scientific-philosophical problem (mind-body problem). What, however, seems indisputable is that each of us exists, survives and develops thanks to the existence of our brain and our body, which allow us to relate to others and the environment. Our nature and way of being specifically human enables our development in a particular culture, which is part of our own education and identity. Of course, this encompasses any kind of religious experience and tradition, but it is surely hard to defend that such a variety of religious practices would be possible, certainly, without a human brain.

Thus, human life and existence, as well as personality, identity and freedom cannot exist in the abstract but only embodied in the concrete person who can perceive and appreciate himself/herself in relation to others when the brain and mind work properly, allowing him/her to reason and relate harmoniously with the human environment (family, society, work and so on) that surrounds him/her and the contingent environment. In this sense, we can say that the brain and mind properly integrated, are fundamental elements of the person. In other words, they are conditions of possibility for the existence, enjoyment and development of human rights. Before further dwelling on the connection between human rights, neuroscience and religion, in the section of this work, we will look into more details with the overlapping that this discussion has with the law.

3. Biolaw and Human Rights

Il Law studies and deals with regulating human behavior insofar as it affects coexistence in society and affects the common good of citizens. Modern neurotechnologies, on the other hand, offer growing knowledge about the human brain and mind, as well as about the behavior of human beings. Both law and neuroscience aim to study human behavior, although each of them uses different tools and perspectives because they do so with different purposes. Both branches of knowledge, within their respecting sphere of influence, can and must interrelate to complement each other, putting the person and society at the center.

Nowadays, neurotechnology offers a series of opportunities that allow us to observe and affect, with increasing depth and knowledge of the cause, the brain of people. Neuroimaging techniques allow us to know and study the shape and functioning of the brain with instruments unthinkable until a few decades ago, with a level of accuracy that is drastically increasing. The greater knowledge of the brain (still very distant from being complete and exhaustive) has allowed the development of more and less invasive products and intervention methods, such as certain medications, brain stimulation (invasive and non-invasive), neurosurgery, cell therapy with neural stem cells and even the implants of electronic devices in our brains[3]. These interventions, insofar as they imply human behavior, are the object of many studies by bioethicists and lawyers.

Such neurotechnological advances are produced thanks to scientists, researchers and medical professionals who dedicate themselves passionately and competently to the study of the human brain and from them civil society legitimately hopes that their knowledge and professionalism will benefit the medical, societal and political community in which they work. In a hypertechnological society such as ours, not infrequently there are voices of suspicion towards the purpose, use and intentions of the people that are part of the scientific community, at times due to completely ungrounded reasons, at times due to some legitimate worries of transparency. To avoid the creation of an even more skeptical society, it is thus convenient and necessary that bioethical and biolegal reflection always accompany the new discoveries and the applications of new technologies.

Prudence in the ethical judgment about neurotechnology and the precautionary principle[4] in their implementation, might help us, on the one hand, to diminish or minimize the unfounded fears towards the new and unknown (which sometimes appears to us as a threat) and, on the other, to moderate the euphoria of the successes of technological development, placing neuroscience and neurotechnology within the realm of the achievable rather than the quasi-Olympian dimension of the divine. As highlighted by various experts, "the brain has a special status in human life that supposes that the interventions in this organ provoke concerns that have not been provoked, to the same extent, by other new technologies or interventions [...] the ethical evaluation of this type of interventions begins by considering the reasons we have to assess our brains and the corresponding imperative reasons to intervene when the brain stops working or when it is damaged or diseased. We observed that the mixture of the ethical imperative to alleviate the damages that result from brain

[3] A. LAVAZZA, M.D. GARASIC, *How Non-invasive Brain Stimulation Might Invade Our Sphere of Justice*, in *Journal of Cognitive Enhancement*, 1, 2017, p. 31-38.

[4] L. MARINI, L. PALAZZANI (EDS.), *Il principio di precauzione, tra filosofia, biodiritto e biopolitica*, Rome, Edizioni Studium, 2008.

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damage and the limits of our knowledge about how to achieve it generates a special tension between necessity and uncertainty[5]".

Therefore, when considering the advancements in the field of neuroscience, there is a need to take into account the intentions with which products, procedures or techniques can be studied or developed: for purposes of experimentation, for therapeutic purposes, for recreational purposes or for military purposes. Both the object of these actions, which involve intervention on the human brain, and its purpose are not, and should not be, alien to the legal world, especially in the light of the fact that such behaviors affect social life -hence, the fundamental rights of people and the common good. While interventions that have a therapeutic purpose (to cure) are normally accepted and requested socially, it is not uncommon to fear how some neurointerventions that involve manipulation (to alter certain characteristics of the brain) could lead to unhealthy use of the technology, alter the human condition in questionable manners and generate and exacerbate injustice.

When we speak of law, we can use the term or concept, at least in two different ways: law as a rule (positive law) and law as a legal right. As a "norm", we refer to law as synonymous with "law" that are provisions of the legitimate authority that intervenes and regulates, with obligatory character, human behavior, when the common good is at stake. In this sense, it is said that a lawyer is an expert in law or that ignorance of law does not exempt from compliance. There are positive laws that regulate to a greater or lesser extent the use of neurotechnology (e.g. laws on biomedical research, on medicines, medical devices and implants, on the autonomy of patients and on the protection of privacy or confidentiality, as well as laws that protect personal data and laws on public health protection), but they can quickly become outdated.

As a "legal right", we refer to the right as a basic need for the existence of the person. It is in this sense that we speak of human rights: of the right to life, to integrity or to one's own identity. From this approach to human rights, these needs are the fundamental assets of the person that we must recognize, respect and guarantee the whole of the citizens and, by mandate of them, the authorities of the State. From this perspective, we seek to analyze the extent to which neurotechnology can affect our rights. It is in this second sense of law that we stop now for a moment to reflect on the human rights that are at stake in the use of neurotechnology. If we take a careful look at the UDHR, we find a series of fundamental goods that have already been recognized as universal and that therefore belong both to those who use neurotechnology and to those who do not use them. Both to those who benefit from their direct use and those who do not (either by choice or inaccessibility of various kind). Neuroscience and its neurotechnological applications are, undoubtedly, instruments that, when used correctly (not only based on technical criteria but also with ethical criteria), offer the opportunity to satisfy and promote respect for life, freedom, psychic integrity, the identity of people. All these are human rights. And together with these individual benefits, society as a whole is also favored by scientific and technological advances. However, it is important not to forget that the growing potential of these instruments can also pose a risk and a threat to dignity and to the same essential assets of people and of society itself. It is to this uncharted territory that Marcello Ienca and Roberto Adorno want us to pay attention, and we shall look into that below. First however, we shall highlight the relevance of the principle of responsibility to human rights and neuroethics.

[5] NUFFIELD COUNCIL ON BIOETHICS, *Novel Technologies: Intervening in the Brain*, London, 2013, p. 72.

4. The Principle of Responsibility, Human Rights and Neuroethics

In line with what explained until now, the principle of responsibility[6] could be revealed as a fruitful way of biolegal reflection to face the need of guardianship of the person and the prevention of the damages that neuroscience could cause to the fundamental rights of man. This is the idea basically put forward by Hans Jonas, for whom: "the responsibility is the care of another being when it is recognized as a duty, becoming a "concern" in case the vulnerability of said being is threatened"[7]. The implementation of this principle, therefore, implies a duty to protect also those who are more fragile and unable to defend themselves.

A legislative project -based on the principle of responsibility- should therefore start with a process of identification, assessment and investigation of biotechnological and neuroscientific risk, aimed at identifying the probability of damage, as well as evaluating the effect: pursuing of different objective contexts. On the one hand, this entails great care for the protection of the person and their personal rights; on the other, it does not hinder the development of the investigation.

Therefore, the need to individualize a definition of the principle of responsibility presupposes that, in addition to being a guide to the options in the legislative field, it can be put into practice in the same way as a mandatory principle for judges, so to put them in a position to identify the possible impact and the incidence of neurotechnology on humans[8]. This idea of constant scrutiny -and adaption- of new technology to human beings and back is at the very center of the next section of our work, and we shall look into it next.

5. New Human Rights: How Would Those Affect Informed Consent?

In a recent article that has rightly gained wide international visibility[9], Marcello Ienca and Roberto Andorno stress how, in the course of human history, our mind has always been our last "refuge of personal freedom and self-determination". Obviously, the claim is made on the -until now unquestionable- fact that no matter what kind of restrictions we might have to endure in the world "out there" (e.g. torture), our "internal" emotions and beliefs are free and untouchable.

As mentioned above, neurotechnology might have led us to an era where such certainty has become less stable. Fearing that we might enter this dystopian future in a very proximate time, Ienca and Andorno propose to implement new human rights that would help us protect ourselves from such threat. The suggested rights are the following four:

[6] The conceptualization of the principle of responsibility is that of the German philosopher Hans Jonas, for whom each individual should apply said principle in each action and gesture she does, constantly taking into account the impact that the given action will have on the future of individuals and of humanity as a whole. H. JONAS, *The Imperative of Responsibility: In Search of an Ethics for the Technological Age*, Chicago, 1984.

[7] H. JONAS, *The Imperative of Responsibility: In Search of an Ethics for the Technological Age*, op. cit. p. 81.

[8] TPICE– that stands for Tribunal de Première Instance des Communautés Européennes (European Communities' Court of First Instance) – in the T-13/99 case, has affirmed that "the scientific assessment of risks is commonly defined both at the international level and at the community level, as a scientific process that consists in identifying and characterizing a hazard, while evaluating the exposure it needs to also connote the risks."

[9] M. IENCA; R. ANDORNO, *Towards new human rights in the age of neuroscience and neurotechnology*, in *Life Sciences, Society and Policy,* 13(1), 2017.

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1) The right to cognitive liberty: the right to alter one's mental states through technical means, and the right to refuse to do so.
2) The right to mental privacy: the right to prevent illegitimate access to our brain information.
3) The right to mental integrity: the right of individuals to protect their mental dimension from potential harm.
4) The right to psychological continuity: the right to preserve personal identity and the coherence of the individual's behavior from unconsented modification.

Out of the four, we want to pay particular attention to the right to mental privacy – the one we think it is most immediately at risk of being threatened by neurotechnology. The reason behind our concern is based on the fact that, differently from the other three rights, this is more "passive" in a sense: it would "only" require a reading from external entities of our brain activity (recent advancements in neuroimage techniques suggest that enormous progress has been made in that direction). The posed threat then, would be twofold: on the one hand, we will risk losing sensitive, personal information, and, on the other, we might suffer so without our informed consent. As this scenario comes close to reality, we feel that it is useful to consult, no matter how preliminarily, historic religious and cultural traditions across the globe to attempt to clarify if and how they might have a common stand among them and with seculars on this timely theme.

6. New Human Rights, Informed Consent and Religion

Could we convincingly define how should or do religions and cultures interact with the advancements of neuroscience? Probably not in a definitive manner, and surely not within the scope of this paper. Yet, we think that the following sections (divided into each religious tradition) will be useful to create a valuable framework within which to build and foster the discussion on the implementation of the new human rights proposed by Ienca and Andorno -with particular emphasis on mental privacy due to its connection with informed consent (or its possible absence).

Buddhism

While some have argued that human rights conflict with the Buddhist approach that sees the *dharma*'s allocation of different duties to different people, others have defended[10] that the way human rights have been formulated is complementary to moral values present in classical Buddhism -hence the current formulations of human rights complement moral values of classical Buddhism and describe what is due under *dharma*.

In relation to the right to mental privacy, as the Buddhist tradition does not strictly rely on individual autonomy (and as a result informed consent), its relevance does not seem so clear. Ellen Zhang provides us with a very important reading of the practical value of the informed consent forms, and the role of duty in the Buddhist tradition. "While Buddhism challenges an individual-oriented approach to autonomy, it also challenges an individual-oriented approach to rights. Buddhism would accept

[10] D. KEOWN; C. PREBISH; W.R. HUSTED (eds.), *Buddhism and human rights*, Richmond/Surrey, 1998.

'negative rights' as a protective means for the interests of the patient yet having problems with using the language of rights without qualification to grapple with every moral issue[11]".

As a result, one might be tempted to think that Buddhism would not be too concerned with the introduction (or not) of a right to mental privacy so to preserve our individual freedom, as not so valued in the Buddhist tradition. However, Hongladarom[12] reminds us that, for Buddhist, much importance must be given to interdependence and compassion, and that those entail care for those who need special protection and respect due to their conditions that make them vulnerable. Hence a protection of the vulnerable (those unable to be in a position to say no) would suggest a support of this defense of informed consent.

Christianity

In relation to the connection between (new) human rights and Christianity[13], Laura Palazzani stresses the importance to keep in mind the connection between rights and duties, highlighting how such a relationship has been developed in the course of the last decades. She writes:

"Within the context of the Catholic Church the line of thought of the relationship between religion and human rights was further elaborated in the documents of the Pontifical Commission 'Iustitia ed Pax', and in particular in the document *The Church and the rights of man* 1975, reprinted in 2011.[14] The document stresses the need to strictly correlate rights and duties – "to speak of rights is like enouncing duties" – and on the widening of rights and duties from the individual to the community, both as far as concerns civil and political rights and economic, social and cultural ones. In the international theological Commission two texts with particular reference to human rights were drafted. Dignity and rights of the human person (1983) stresses the need to clearly define man's rights and to establish their juridical formulation, with a view to a common interpretation of the rights of man, at least in political and social terms. In the document In search of a universal ethic: a new look at the natural law (2009) the urgent need to reinterpret natural law, natural right and human rights in the context of religious and philosophical pluralism, secularization and the recent historical-social transformations, particularly with regard to techno-scientific development, are addressed[15]".

Of extreme importance, is also the call for attention towards the corresponding duties that one has when receiving rights that the Pontifical Council for Peace and Justice has repeatedly and strongly

[11] E. ZHANG, *Informed consent – A Critical Response from a Buddhist Perspective*, in *Studia Bioethica*, 11 (2), 2018, pp. 5-13.

[12] S. HONGLADAROM, *Buddhist perspective on four vulnerable groups: Children, women, the elderly and disabled*, in P.J. THAM; A. GARCIA; G. MIRANDA (eds.), *Religious perspectives on human vulnerability in bioethics*, Dordrecht, 2014, p. 117-133.

[13] Although aware of the fact that we refer to Christianity only through the lenses of Roman Catholicism, we are convinced that the positions here highlighted do not clash in any way with the Christian Orthodox, Protestant and other version of Christian bioethics. K. WILDES, *The Ecumenical and Non-Ecumenical Dialectic of Christian Bioethics*, in *Christian bioethics: Non-Ecumenical Studies in Medical Morality*, 1 (2), Oxford University Press, 1995, pp. 121-127.

[14] These documents do not coincide with the official position of the Church but constitute a significant contribution to its internal reflection.

[15] L. PALAZZANI, *The Christian-Catholic Religious Perspective: Human Rights, Cultural Pluralism and Bioethics*, in J. THAM; K. KWAN; A. GARCIA (eds.), *Religious Perspectives on Bioethics and Human Rights*, Cham, Switzerland, 2017, pp. 190-191.

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stressed. In the Compendium of the Social Doctrine of the Church,[16] as a matter of fact, it says: "Therefore those who, while claiming their rights, forget or do not place their respective duties in the right place, run the danger of building with one hand and destroying with the other[17]".

More specifically still for the scope of the present investigation, Palazzani goes on to explain in another work, the Christian approach to the right to mental privacy, stressing that: "informed consent is inspired by Jesus, who cured the sick with compassion, generosity, and understanding. Christians believe that disease and suffering are trials from God to bring them closer to salvation through death and into His grace. Scientific research should be done for the purpose of serving those who are ill, not solely or primarily for the benefit of the researchers[18]". Hence, the need to implement the new human rights suggested appears necessary. Not only they would guarantee the continuation of this integration between rights and duties so relevant and central for the Christian tradition, but - concerning the specific right to mental privacy- it would preserve the theological space that informed consent requires for the believer to freely choose to follow the path of Jesus. Any alteration that could jeopardize the genuineness of such a choice could not been seen favorably by the tradition and must then by avoided at all costs by implementing the required normative tools that help us defend ourselves from such a threat.

Confucianism

There is no clear concept of human rights in early Confucian societies, possibly because, instead of laws, such societies were governed more often by rites. It was this very ritual based governing scheme that decided who had to do what. Despite the fact that modern China has not fully pledged its commitment to the UDHR, there are numerous ideas related to human rights embedded within Confucianism that have been implemented by recent governments.

Ruiping Fan explains how, in strict medical sense, the relevance of informed consent might not be as important as it should be when considering the value of expressing one's ideas in political terms, as politics is always more important than medicine when considering the benefits that could be done to society. Yet the result, in terms of the right to mental privacy appear to be the same. He writes: "Confucianism sees medicine as 'the art of *ren*'[19] […] Throughout the history of Chinese medicine, the emphasis has always been placed on the physician's virtue and obligation in performing the art of *ren* for assisting people, rather than on providing adequate information to patients and their families. In reality, Chinese physicians must have gained consent, either explicitly or implicitly, from patients and their families in order to conduct medical treatment, but it is also clear that obtaining such consent before treatment has never been formally and clearly required in the tradition[20]". Even if not so easy to predict for all four of the newly proposed human rights, it would appear as if the Confucian tradi-

[16] www.vatican.va/roman_curia/pontifical_councils/justpeace/documents/rc_pc_justpeace_doc_20060526_compendio-dott-soc_it.html#c)%20Diritti%20e%20doveri (last visited 14/04/2019)

[17] GIOVANNI XXIII, Lett. enc. *Pacem in terris*: AAS 55 (1963) 264.

[18] L. PALAZZANI, *Multicultural and interreligious perspectives on informed consent. The Christian perspective*, in *Studia Bioethica*, 11 (2), 2018, pp. 14-22.

[19] "Ren" could mean: 'humanity', 'humaneness', 'goodness', 'benevolence', or 'love'.

[20] R. FAN, *A Confucian View of Informed Consent and the Issue of Vaccination*, in *Studia Bioethica*, 11 (2), 2018, pp. 23-30.

tion would not see positively the possibility to direct one's consent -be it individual or collective- as this represent a path to virtue for the individual, families and society.

Hinduism

Although India is the largest democracy in the world and Mahatma Gandhi is considered by many as an example of civil rights, such rights do not fully accommodate themselves in the Hindu tradition. "As Hajime Nakamura, a Buddhist and Hindu scholar says, "we don't usually speak of rights in our tradition," referring to all of the Eastern religions. On the other hand, the religious texts are replete with the concepts of duty, often translated as dharma same as religion. Rights imply entitlements, duties are obligations[21]".

Hence, although, as for other Asian traditions, Hinduism sees the centrality of individual autonomy as much less important than in the West -and with that the relevance of informed consent- the moral acceptance of medical and clinical practices and trials gets its legitimization through a form of relational autonomy (both moral and legal) that requires *some* degrees of freedom of choice and independent processing that the right to mental privacy would guarantee. Yet, the issue seems to be less pivotal than in other traditions perhaps.

Islam

As in the case of China and Confucianism, the UDHR has had some problems in getting implemented in Muslim countries due to the fact that they can only be guaranteed within the Qur'an and Shari'ah law as these tools are necessary for the definition of religious responsibilities and allow authorities to be recognized by the community. For this reason, in 1990 Muslim states created an alternative to the UDHR, the Cairo Declaration on Human Rights in Islam. Later on, in 1994 the Arab Charter on Human Rights more closely approximated "a global bioethics that invokes the western conception of human dignity with subsequent rights and resultant duties and directly affirms the UN Declaration of Human Rights[22]".

Aasim Padela stresses further the importance of understanding the reason behind a partial acceptance of the UDHR as a response to a perception of a "Western imposition" that pushes Muslim states to look at the document with skepticism. He writes: "Just as medical technology and curricula are patterned after Western academies, bioethics teaching around the world also draws upon ethical principles and moral frameworks first worked out in the "West."[23] […] Given the scant literature that is available on informed consent practices in Muslim contexts, these trends suggest that informed consent processes and structures likely mimic implementation models within the US and Europe. [I want to] draw attention to a couple of features of Muslim culture that problematize such consent

[21] P.N. DESAI, *Duties and Rights in Hinduism: Before and After India's Independence*, in P. J. THAM; K. KWAN; A. GARCIA (eds.), *Religious Perspectives on Bioethics and Human Rights*, Cham, Switzerland, 2017, p. 155.

[22] A. GARCIA; J. LUNSTROTH; D.J. MONLEZUN; C.R. SOTOMAYOR, *Convergence of Human Rights and Duties: Towards a Global Bioethics*, in J. THAM; K. KWAN; A. GARCIA (eds.), *Religious Perspectives on Bioethics and Human Rights*, Cham, Switzerland, 2017, p. 69.

[23] R. DE VRIES; L. ROTT, *Bioethics as Missionary Work: The Export of Western Ethics to Developing Countries,* in C. MYSER (ed.), *Bioethics around the Globe*, New York, 2011, p. 3-18.

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processes and thereby necessitate a re-imagining of these procedures to suit Muslim sensibilities and culture[24]".

Those features include the fact that Muslim societies operate out of a communitarian ethos and shared decision-making processes and that, for such societies, there is a need to ground ethics regulations within Islamic law -including during the implementation of informed consent processes. What Padela is suggesting then is that, within Islam, we might reach the same results through a different path (perhaps based on less individual centered version of autonomy). However, as in other traditions where the value of individual informed consent might not be as predominant as in the secular Western context, it seems that the very reference to a concept of duty towards the vulnerable, as well as the quasi-dignity referred in the Arab Charter on Human Rights would push Islamic ethicists to support the right to mental privacy with conviction.

Judaism

As in the case of other traditions, the relationship between rights and duties is of crucial importance in the Jewish tradition, and David Heyd explains to us the approach that Judaism has towards human rights along those lines. He writes: "Rights as we understand them are the product of seventeenth-century philosophical culture in Europe. It is a modern concept. But beyond that, even after its integration in modern liberal worldview, it has not been easily incorporated in religious thought in general and that of Judaism in particular. For rights are claims that human beings have against each other, or against the state; but it would be absurd to make claims against God. Rights particularly call for the protection of the interests of an individual from competing interests of other individuals (or the state); but God has no competing interests against which a human being must be protected. Rights are not derived from duties but rather impose duties on others.[25] Obviously, human beings cannot impose duties on God and hence can have no rights against Him. Rights are characteristically mutual, that is people have at least the same human rights against each other. But this reciprocity cannot apply to the relation between humans and God. There is something intrinsically alien in the concept of rights in the sphere of religious, duty-based ethics[26]".

This seems particularly relevant and interesting to consider when elaborating a possible common stand from religions and cultural traditions in relation to the newly proposed human rights. First, it stresses the way in which rights are to be claimed against other individuals, the state or third entities (e.g. internet companies?), second, it makes a link between rights and duties that perhaps is key in relation to this new human rights in particular: the duty not to interfere with some of our more intimate and personal ways of existing (of course, particularly in some traditions, this idea of not interfering with God's work has had a historically revisited approach to it (Heyd clearly stresses how Judaism changed in time its attitude towards intervening medicine), but perhaps this is something altogether new and hence in need to be defended more fiercely. What remains crucial to ensure, is the absence of a structural interference by other in our freedom to be informed and decide.

[24] A. PADELA, *Reflecting and Adapting Informed Consent to fit within an Islamic Moral Landscape and in Muslim Contexts*, in *Studia Bioethica*, 11 (2), 2018, pp.31-39.

[25] J. RAZ, *The Morality of Freedom*, Oxford, 1986, p.1 81.

[26] D. HEYD, *Between Humaneness and Human Rights: A Jewish Perspective on Modern Bioethics*, in J. THAM; K. KWAN; A. GARCIA (eds.), *Religious Perspectives on Bioethics and Human Rights*, Cham, Switzerland, 2017, p. 260.

7. Conclusions

In conclusion, it appears that the implementation of a new, additional human right -that of mental privacy- would be seen favourably by all traditions considering not only their respective quasi-univocal acceptance of the UDHR, but rather for the shared concern of the importance of complying with a duty towards oneself and the community (be it religious or secular). In that light, any technological advancement that could alter significantly our capacity to act otherwise (these are the main concerns put forward by Ienca and Andorno) should be approached with extreme caution -and the introduction of new human rights seem to be a great and needed way forward for our global community. Hence, we have highlighted how six of the main religious traditions would generally agree in supporting extreme caution with all applications related to neurotechnological advancements, particularly in relation to the right to mental privacy and the threat informed consent might suffer from its lack of implementation.

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Special issue

New Strategies for Increasing Participation of Patients from Diverse Cultural and Religious Backgrounds in Clinical Trials

Laura Palazzani, Fabio Macioce, Margherita Daverio, Loredana Persampieri, Valeria Ferro*

ABSTRACT: Cultural differences between researchers and potential participants in clinical trials could result in communication barriers, which are likely to hinder awareness and pose challenges to the informed consent process. An intercultural communication approach to the informed consent process could facilitate potential participants' understanding; strategies such as the involvement of family members, cultural insiders, cultural mediators during the consent process should be adopted to overcome language and cultural barriers. The article highlights as well barriers related to the interaction between gender and multicultural issues in cross-cultural communication and stresses some culturally-sensitive strategies for the inclusion of pregnant women in clinical research. Consent procedures tailored to local cultural patterns with a focus on the use of new technologies are discussed.

KEYWORDS: Informed consent; intercultural communication; community engagement; gender; ICT

SUMMARY: 1. Introduction – 2. The informed consent process involving participants from diverse cultural and religious backgrounds: barriers and challenges to global clinical research – 2.1. Communication barriers to recruitment of research participants in international multicenter and multicultural clinical trials – 2.2. Reconciling autonomy with community: an intercultural approach to communication – 2.3. Elements for an interculturally-sensitive informed consent – 3. Interaction between gender, culture and education in cross-cultural communication – 3.1. Gender and health literacy – 3.2. Culturally-sensitive communication for the inclusion of pregnant women in clinical trials – 3.3. The role of the male partner in the informed consent process – 3.4. Best practices on culturally-tailored health communication programs with a gender perspective – 4. Strategies to overcome communication barriers between researchers and research participants – 4.1. Cultural competence training for researchers working with subjects from diverse cultural and religious backgrounds – 4.2. Innovative strategies to improve the informed consent process in an intercultural setting – 4.3. Ethical challenges related to the use of ICT and social media in clinical research: e-Consent in an intercultural setting.

* *Laura Palazzani, Professore Ordinario di Filosofia del Diritto, Libera Università Maria Ss. Assunta (LUMSA), Roma. E-mail: palazzani@lumsa.it; Fabio Macioce, Professore Ordinario di Filosofia del Diritto, Libera Università Maria Ss. Assunta (LUMSA), Roma. E-mail: fmacioce@libero.it; Margherita Daverio, ricercatore Libera Università Maria Ss. Assunta (LUMSA), Roma. E-mail: m.daverio@lumsa.it; Loredana Persampieri, ricercatore Libera Università Maria Ss. Assunta (LUMSA), Roma. E-mail: l.persampieri@lumsa.it; Valeria Ferro, ricercatore Libera Università Maria Ss. Assunta (LUMSA), Palermo.* E-mail: *v.ferro@lumsa.it. The article was subject to a double-blind peer review process.*

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1. Introduction

The purpose of this literature and ethical guidelines' review is to consider cultural challenges in the informed consent process, in order to increase participation of people of different cultures and religious beliefs. By "increasing participation", we mean focusing on avoiding an unfair exclusion of subjects from diverse cultural backgrounds (and religious, insofar as religion influences culture generating communication barriers, that can cause someone not to participate in a clinical study due to their religious beliefs) from clinical research. Cultural diversity includes several cultural elements that can affect health, such as nutrition, gender differences, the family structure, the concepts of autonomy and solidarity. The objective of this contribution is to make sure that cultural/language barriers in the communication process do not exclude these populations from accessing potential benefits, in those cases where they are envisaged in the study design. Overcoming culturally-driven communication challenges may ultimately lead to an improved access to research participation. Therefore, we will discuss an intercultural approach to communication and a participatory approach to the informed consent process (e.g. taking into account the perspectives of different cultural groups in the development of information materials, etc.). This approach can empower culturally-diverse subjects to make autonomous decisions with regard to their participation/non-participation in clinical research. The analysis of findings focuses also on verifying whether reliance on technological developments in information, which offer new opportunities for the implementation of informed consent, as well as the selection of digital tools according to cultural patterns, may help to modernize and improve the informed consent process, overcoming possible communication barriers between researchers and participants in clinical trials.

2. The informed consent process involving participants from diverse cultural and religious backgrounds: barriers and challenges to global clinical research

2.1. Communication barriers to recruitment of research participants in international multicenter and multicultural clinical trials

Informed consent is not only a written form or a bureaucratic procedure, but also, above all, an essential communication process between the participant and the researcher in clinical research. In many cases, obtaining informed consent may be difficult with people from diverse cultural and religious backgrounds, as it is in the case of international multicenter studies where researchers and the potential participants belong to different cultural contexts[1]. In order to overcome communication barriers and avoid misconceptions and misunderstandings, interaction in a multicultural setting cannot overlook cultural diversity[2], as it contributes to shaping subjective identities, thus, it has an impact on the way people process and understand information[3].

[1] H. TEN HAVE, B. GORDIJN (eds.), Handbook of Global Bioethics, Dordrecht, 2013, p. 154.

[2] The UNESCO Universal Declaration on Cultural Diversity, 2001, available at https://unesdoc.unesco.org/ark:/48223/pf0000127162, last visited April 26th, 2019, sets out that "culture takes diverse forms across time and space. This diversity is embodied in the uniqueness and plurality of the identities of the groups and societies making up humankind (…)" (Article 1). It equally stresses that "the defence of cul-

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Cultural differences between researchers and potential participants in clinical trials could result in communication barriers, which are likely to hinder awareness and pose challenges to the informed consent process[4]. In 2015, WHO underlined that **"**a challenge in global health ethics concerns international research, especially where investigators from wealthy countries conduct research in impoverished settings where participants are especially vulnerable or where language and cultural barriers make informed consent difficult**"**[5]. In cross-cultural communication – as in the case of certain international multicenter clinical trials –special care is recommended in collecting informed consent, in order to avoid the risk of possible poor communication due to language differences[6]. The difference of values and beliefs (even if not limited to cases of multicultural settings) could generate difficulties in communication itself[7]: for example, certain cultural practices and expectations may impact negatively on communication to prospective participants in clinical trials, e.g., in some settings the belief that for a medicine to be effective it has to be bitter or it must hurt[8]. Sound comprehension of infor-

tural diversity is an ethical imperative, inseparable from respect for the dignity of the human person" (Article 4). Culture refers to the set of spiritual and material, intellectual and affective traits that characterize a society or a social group (see UNESCO Universal Declaration on Cultural Diversity, 2001, cit., Preamble); moreover, it "encompasses in addition to art and literature, lifestyles, ways of living together, value systems, traditions and beliefs" (see UNESCO Universal Declaration on Cultural Diversity, 2001, cit.). It is important to keep in mind that cultural diversity and religious diversity do not overlap, as in the same cultural group one can find different religious beliefs, and the same religious group can embrace diverse cultural patterns.

[3] As highlighted by the Italian Committee for Bioethics, cultural backgrounds influence individual and collective behaviours: in the researcher-participant relationship, the researcher acts according to his/her heritage of knowledge grounded in medical and professional education/experience gained in particular cultural and social contexts, whereas culturally heterogeneous participants may carry with them a broad spectrum of cultural values and religious beliefs, which influence their lifestyles, health habits and views of medical interventions and therapies, different understandings of modesty in public areas, and more generally, different philosophical interpretations of medical duties, goals and practices (i.e. diverse concepts of health, illness, disease, corporeity) (see ITALIAN COMMITTEE FOR BIOETHICS (NBC), Opinion on Migration and Health, 2017, available at http://bioetica.governo.it/en/works/opinions-responses/migration-and-health/, last visited April 8th, 2019).

[4] D. SCHROEDER, J. COOK, F. HIRSCH, S. FENET, V. MUTHUSWAMY, *Ethics Dumping Case Studies from North-South Research Collaborations*, New York, 2018, pp. 134.

[5] WHO, *Global Health Ethics. Key issues*, 2015, available at https://www.who.int/ethics/publications/global-health-ethics/en/, last visited March 25th, 2019 .

[6] UNESCO INTERNATIONAL BIOETHICS COMMITTEE (IBC), Report of the IBC on Consent, 2008, available at https://unesdoc.unesco.org/ark:/48223/pf0000178124, last visited March 25th, 2019; THE COUNCIL OF EUROPE, *Guide for Research Ethics Committee Members, Steering Committee on Bioethics*, April 2012, https://www.coe.int/t/dg3/healthbioethic/activities/02_biomedical_research_en/Guide/Guide_EN.pdf, last visited March 25th, 2019; CIOMS, *International Ethical Guidelines for Epidemiological Studies*, 2009, available at https://cioms.ch/wp-content/uploads/2017/01/International_Ethical_Guidelines_LR.pdf, last visited March 25th, 2019; CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, Geneva, 2016, https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf, last visited March 25th, 2019.

[7] EGE, Ethical aspects of clinical research in developing countries. Opinion n. 17, 2003, available at https://publications.europa.eu/en/publication-detail/-/publication/6339dcbf-c156-4e7f-9e43-9928acf82118/language-en/format-PDF/source-77404483, last visited March 25th, 2019.

[8] CIOMS, Drug development research in Resource-Limited Countries. How to succeed in implementation of Good Clinical Practice Guidelines. Draft report of the Joint CIOMS/WHO Working Group, CIOMS, Geneva, December 2005, available at https://cioms.ch/wp-content/uploads/2017/05/DrugDevelopRpt14Dec2005.pdf, last visited March 3rd, 2019.

mation can moreover become complex when those who intervene do not use the same references in approaching health problems (for example, the scientific approach of a research team is different from a mystic, supernatural approach to health which could be found in some communities)[9].

Main barriers in cross-cultural communication can be identified with language barriers[10]; as a matter of fact, in some communities, there could not even be the word to express some scientific concepts related to research, e.g. for the term 'randomization'[11]. Other barriers can concern a lack of awareness about trials and in particular poor understanding of the concept of research, which may be confused with the direct health services provision[12], and with a lack of trust in researchers and low health literacy regarding immunization; concern about adverse events and fears about exploitation (especially in the case of healthy volunteers, as it is in the case of experimental vaccines)[13].

In this review, we will focus mainly on language barriers. If not addressed, communication barriers between the participants and the researchers may influence comprehension of potential benefits

[9] UNESCO INTERNATIONAL BIOETHICS COMMITTEE (IBC), Report of the IBC on Consent, 2008, available at https://unesdoc.unesco.org/ark:/48223/pf0000178124, last visited March 25th, 2019.

[10] J. BODDY, *Research across cultures, within countries: Hidden ethics tensions in research with children and families?*, in *Progress in Development Studies*, 14(1), 2014, pp. 91-103; P. AMORRORTU ET AL., *Recruitment of racial and ethnic minorities to clinical trials conducted within specialty clinics: an intervention mapping approach*, in *Trials* 19, 2018, p. 115; L. CONDON ET AL., *Engaging Gypsy, Roma, and Traveller Communities in Research: Maximizing Opportunities and Overcoming Challenges*, in *Qualitative Health Research*, 2019, available at https://www.ncbi.nlm.nih.gov/pubmed/30600758; D. SCHROEDER, J. COOK, F. HIRSCH, S. FENET, V. MUTHUSWAMY, *Ethics Dumping Case Studies from North-South Research Collaborations*, cit., pp. 99-106; L. PALAZZANI, *Innovation in Scientific Research and Emerging Technologies. A Challenge to Ethics and Law*, Cham (Switzerland), 2019, pp. 157.

[11] G. OKELLO ET AL., *Challenges for consent and community engagement in the conduct of cluster randomized trial among schoolchildren in low-income settings: experiences from Kenya*, in *Trials* 14, 2013, p. 142. In addition, a study from UK about the inclusion of non-English-speaking patients in research reported language barriers and the unavailability of translators for different reasons (R. BERNIER, E. HALPIN, S.J. STAFFA, L. BENSON, J.A. DI NARDO, V.G. NASR, *Inclusion of non-English-speaking patients in research: A single institution experience*, in *Paediatric Anaesthesia Journal*, 28(5), 2018, pp. 415-420).

[12] This could result in difficulties in understanding research process in general (see J. BODDY, *Research across cultures, within countries: Hidden ethics tensions in research with children and families?*, in *Progress in Development Studies*, cit.; S. GEORGE, N. DURAN, K. NORRIS, *A systematic review of barriers and facilitators to minority research participation among African Americans, Latinos, Asian Americans, and Pacific Islanders*, in *American Journal Public Health*, 104(2), 2014, pp. 16-31; T.W. QUAY ET AL., *Barriers and facilitators to recruitment of South Asians to health research: A scoping review*, in *British Medical Journal Open*, 2017, available at https://bmjopen.bmj.com/content/bmjopen/7/5/e014889.full.pdf, last visited May 5th, 2019; P. AMORRORTU ET AL., *Recruitment of racial and ethnic minorities to clinical trials conducted within specialty clinics: an intervention mapping approach*, cit.; L. PALAZZANI, *Innovation in Scientific Research and Emerging Technologies. A Challenge to Ethics and Law*, Cham (Switzerland), cit., pp. 16-17.

[13] J. BODDY, *Research across cultures, within countries: Hidden ethics tensions in research with children and families?*, cit.; T.W. QUAY ET AL., *Barriers and facilitators to recruitment of South Asians to health research: A scoping review*, cit.; P. AMORRORTU ET AL., *Recruitment of racial and ethnic minorities to clinical trials conducted within specialty clinics: an intervention mapping approach*, cit.; J.L. BROWNE, C.O. REES, J.J.M. VAN DELDEN ET AL., *The willingness to participate in biomedical research involving human beings in low- and middle-income countries: a systematic review*, in *Tropical Medicine & International Health,* 24(3), 2019, pp. 264-279; S. GEHLERT, J. MOZERSKY, *Seeing Beyond the Margins: Challenges to Informed Inclusion of Vulnerable Populations in Research*, in *The Journal of Law, Medicine & Ethics*, 46, 2018, pp. 30-43; B. BODEN-ABALA ET AL., *Examining Barriers and Practices to Recruitment and Retention*, in *Stroke Clinical Trials*, 46(8), 2015, pp. 2232-7.

and risks related to clinical studies[14], leading to misconceptions with respect to an overestimation of envisaged benefits deriving from inclusion in a clinical trial (the so-called "therapeutic misconception")[15] or, in general, the expectation of receiving health services in the context of severely resource-constrained public health systems[16].

2.2. Reconciling autonomy with community: an intercultural approach to communication

International guidelines for scientific research involving humans recommend individual, free and informed consent as a general ethical standard[17]. The same ethical guidelines highlight that consent presents always a social and cultural context that must be taken into account and respected[18]. This is particularly important in the case of some international scientific research, where subjects with different cultural backgrounds are involved in clinical trials, at least as potential participants. As a matter of fact, there are cultures in which the community perspective can prevail on individual informed consent[19]; or there are communities, such as some south Asian ones, where there are decisional hierarchies within families[20]; moreover, in many settings community leaders or family members play

[14] J. BODDY, *Research across cultures, within countries: Hidden ethics tensions in research with children and families?*, cit.; G. BERNAL ET AL., *Methodological challenges in research with ethnic, racial, and ethnocultural groups*, in F.T.L. LEONG ET AL. (Eds.), *APA handbook of multicultural psychology, Vol. 1. Theory and research*. Washington, DC, 2014, pp. 105-123; T.W. QUAY ET AL., *Barriers and facilitators to recruitment of South Asians to health research: A scoping review*, cit.; P. AMORRORTU ET AL., *Recruitment of racial and ethnic minorities to clinical trials conducted within specialty clinics: an intervention mapping approach*, cit.; R. BERNIER ET AL., *Inclusion of non-English-speaking patients in research: A single institution experience*, cit.

[15] P. MARSHALL, UNICEF/UNDP/WORLD BANK/WHO SPECIAL PROGRAMME FOR RESEARCH AND TRAINING IN TROPICAL DISEASES & WORLD HEALTH ORGANIZATION, *Ethical challenges in study design and informed consent for health research in resource-poor settings*, 2007, available at http://www.who.int/iris/handle/10665/43622, last visited March 1st, 2019; L. PALAZZANI, *Innovation in Scientific Research and Emerging Technologies. A Challenge to Ethics and Law*, cit.

[16] P. AMORRORTU ET AL., *Recruitment of racial and ethnic minorities to clinical trials conducted within specialty clinics: an intervention mapping approach*, cit.

[17] WORLD MEDICAL ASSOCIATION, *Declaration of Helsinki*, 1964 last version 2013, available at https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/, last visited April 8th, 2019; CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, Geneva, 2016, cit.

[18] UNESCO INTERNATIONAL BIOETHICS COMMITTEE, *Diversity of cultural expressions*, 2005, available at https://en.unesco.org/creativity/sites/creativity/files/article_18en.pdf, last visited March 25th, 2019; UNESCO INTERNATIONAL BIOETHICS COMMITTEE (IBC), *Report of the IBC on Consent*, 2008, available at https://unesdoc.unesco.org/ark:/48223/pf0000178124, last visited March 25th, 2019; CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, cit.; P. MARSHALL, *Ethical challenges in study design and informed consent for health research in resource-poor settings*, cit.

[19] P.E. EKMEKCI, B. ARDA, *Interculturalism and Informed Consent: Respecting Cultural Differences without Breaching Human Rights*, in *Cultura (Iasi)*, 14(2), 2017, pp. 159-172; C. T. ANDOH, *African Communitarian Bioethics and the Question of Paternalism*, in *British Journal of Education, Society & Behavioural Science*, 15(4), 2016, pp. 1-16.

[20] T.W. QUAY ET AL., *Barriers and facilitators to recruitment of South Asians to health research: A scoping review*, in *British Medical Journal Open*, 2017, available at https://bmjopen.bmj.com/content/bmjopen/7/5/e014889.full.pdf, last visited May 5th, 2019.

an important role in the decision-making process for participation in research[21]. To respond to this challenge, **"**it is necessary that the issue of consent be envisaged in a more global context of education, making persons autonomous whilst keeping in mind the primacy of the interests of the person concerned in their social setting. It is necessary to ensure the respect for the will of the person concerned, and to promote education towards autonomy and individual responsibility**"**[22]. This aim can be achieved through an improved intercultural communication in the informed consent process. An intercultural communication presupposes embracing intercultural bioethics as the underlying theoretical framework through which to interpret and understand a culturally-sensitive communication, preventing communication barriers, as far as possible, or re-thinking ways to overcome them, by taking into account the intercultural perspective. Interculturalism values cultural diversity and pluralism, alongside emphasizing integration and social inclusion. As the UNESCO *Declaration on Cultural Diversity* points out **"**no one can invoke cultural diversity to threaten human rights guaranteed by international law, nor to limit their scope**"**[23], and it makes clear that **"**everyone must be able to participate in the cultural life of his choice, and exercise its forms, within the limits imposed by respect for human rights and fundamental freedoms**"**[24].

In an intercultural approach to communication, it is crucial to overcome stereotypical thinking and a "one for all" communication method, devoting attention to the cultural backgrounds of patients or research participants and to personal specificity among individuals belonging to same culture, contributing to the achievement of a more respectful, complete and effective informed consent process. Starting from the knowledge of the cultural tradition researchers face with, respect is recognized as one of the ethical principles of conduct in research in general, but in particular in research in developing countries[25]; anything in the nature of the research which the participant may find morally or culturally sensitive should entail some corresponding sensitivity in obtaining consent (see Singapore's Bioethics Advisory Committee (BAC), *Ethics Guidelines for Human Biomedical Research* (2015). Besides, the ways of conveying information should be adapted and tailored[26]. Information should be

[21] P. MARSHALL, *Ethical challenges in study design and informed consent for health research in resource-poor settings*, cit., p. 6 and pp. 27-31.

[22] UNESCO INTERNATIONAL BIOETHICS COMMITTEE (IBC), *Report of the IBC on Consent*, 2008, cit., III.3.3, n. 120.

[23] UNESCO, *Universal Declaration on Cultural Diversity*, 2001, cit., article 4.

[24] UNESCO, *Universal Declaration on Cultural Diversity*, 2001, cit., article 5.

[25] TRUST Project, *Global Code of Conduct for Research in Resource-Poor Settings*, 2018, available at http://www.globalcodeofconduct.org/wp-content/uploads/2018/05/Global-Code-of-Conduct-Brochure.pdf, last visited on March 1st, 2019; L. PALAZZANI, *Innovation in Scientific Research and Emerging Technologies. A Challenge to Ethics and Law*, cit.

[26] EGE remarks that the way information is given to patients and the procedure of obtaining consent may vary according to the specific situation of the country where a clinical trial takes place, namely regarding the level of literacy, the level of scientific understanding, the organisation of the community, etc. that may influence the consent procedures regarding the involvement of persons, in particular women, in a clinical trial (see EGE, *Ethical aspects of clinical research in developing countries. Opinion n. 17*, 2003, available at https://publications.europa.eu/en/publication-detail/-/publication/6339dcbf-c156-4e7f-9e43-9928acf82118/language-en/format-PDF/source-77404483; L. PALAZZANI, *Innovation in Scientific Research and Emerging Technologies. A Challenge to Ethics and Law*, cit.).

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given in a culturally appropriate way[27]. An intercultural approach to communication should be adopted in all cases where there is cultural diversity between the research team and prospective research participants, insofar as this diversity becomes challenging in terms of communication effectiveness and affects the latter's autonomous decision-making throughout the entire informed consent process (before, during, and after the end of a clinical study, in the sense of having the proper information to be able to decide whether to participate in a clinical study, stay in or leave the study at any time without any form of retaliation, an adequate understanding of what is at stake, in terms of benefits and risks, as well as of required behaviours after the end of the study to protect participants' health). This approach to communication involves a global perspective; namely, it can apply both to clinical research conducted within Europe with participants from diverse cultural backgrounds, and clinical research beyond Europe (including but not limited to developing countries).

Potential participants' comprehension can be enhanced by researchers through previous consultation with cultural mediators and local representatives regarding the most effective ways of communicating the purpose of the study; investigators might consider conducting focus groups with representatives of those who may be recruited to a study, in order to understand issues and concerns associated with preparing the consent form and developing approaches to obtain consent[28]. In addition, adopting strategies to safeguard the understanding of the nature and the implications of the research, such as including sufficient time for subjects to consider their participation and discuss it with family and friends; provision of adequate information about what research entails (about research in general and the specific research in particular) from someone without a dependency relationship (such as between physician and patient)[29]. Establishing trust is also an important element, alongside with building long-term relationships between the community and the research team[30]. It should be equally underlined that in obtaining consent, in some cases, it may be appropriate to obtain before an agreement from the community or from a family member. If a person does not wish to partici-

[27] UN-REDD PROGRAMME, *Guidelines on Free, Prior and Informed Consent*, 2013, available at https://www.uncclearn.org/sites/default/files/inventory/un-redd05.pdf, last visited April 26th, 2019; UNESCO, *Policy on engagement with indigenous people*, 2018, available at https://unesdoc.unesco.org/ark:/48223/pf0000262748, last visited March 1st, 2019. In relation to intercultural communication in the specific case of vaccinations WHO, *Zika Strategic Response Plan*, 2016, available at https://www.who.int/emergencies/zika-virus/strategic-response-plan/en/, last visited March 1st, 2019.

[28] P. MARSHALL, *Ethical challenges in study design and informed consent for health research in resource-poor settings*, cit.; K. CHATFIELD ET AL., *Research with, not about, communities – Ethical guidance towards empowerment in collaborative research*, a report for the TRUST project, 2018, available at http://trust-project.eu/wp-content/uploads/2018/07/TRUST-Community-Participation-in-Research-Final.pdf, last visited March 1st 2019.

[29] J.L. BROWNE, C.O. REES, J.J.M. VAN DELDEN, ET AL., *The willingness to participate in biomedical research involving human beings in low- and middle-income countries: a systematic review*, cit.

[30] P. MARSHALL, *Ethical challenges in study design and informed consent for health research in resource-poor settings*, cit.; J.J.M. VAN DELDEN, R. VAN DER GRAAF, *Revised CIOMS International Ethical Guidelines for Health-Related Research Involving Humans*, in *Journal of the American Medical Association,* 317(2), 2017, pp. 135-136; P. AMORRORTU ET AL., *Recruitment of racial and ethnic minorities to clinical trials conducted within specialty clinics: an intervention mapping approach*, cit.; K. CHATFIELD ET AL., *Research with, not about, communities – Ethical guidance towards empowerment in collaborative research, a report for the TRUST project*, 2018, cit.

pate, his/her will must always be respected[31]. A 'relational' view of autonomy, which includes in the autonomy of the individual also the reference to dialogue with the researcher/physician as well as with wife/husband/relatives[32] can provide solutions to ethical and practical problems in clinical practice and research[33].

2.3. Elements for an interculturally-sensitive informed consent

Given the social and cultural context of informed consent recalled above, the informed consent process must take into account some aspects, in order to be interculturally-sensitive. First, through community consultation[34] and other community engagement strategies researchers should verify that informed consent takes into account cultural practices and the health service context. Informed consent procedures should be tailored to local requirements to achieve genuine understanding[35]. Second, one should recall that the process of "back-translation" of the informed consent form (after the translation of the consent form in another language, the form is then given to a native speaker who translates the document back to the original language) is a process which ensures the validity of the translated form and provides opportunities for corrections to be made. Particular attention must be given to the appropriate use of local dialects and terminology that effectively conveys the meanings of words to potential research participants[36]; with some populations, where the language is generally spoken and not written, there could be offered the possibility to read the document in Eng-

[31] EMA, *Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted in third countries and submitted in marketing authorisation applications to the EMA*, 2010, available at https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/draft-reflection-paper-ethical-good-clinical-practice-aspects-clinical-trials-medicinal-products_en.pdf, last visited March1st, 2019; EGE, *Ethical aspects of clinical research in developing countries. Opinion n. 17*, 2003, available at https://publications.europa.eu/en/publication-detail/-/publication/6339dcbf-c156-4e7f-9e43-9928acf82118/language-en/format-PDF/source-77404483, last visited March1st, 2019; TRUST PROJECT, *Global Code of Conduct for Research in Resource-Poor Settings*, 2018, available at http://www.globalcodeofconduct.org/wp-content/uploads/2018/05/Global-Code-of-Conduct-Brochure.pdf, last visited March1st, 2019;

[32] ITALIAN COMMITTEE FOR BIOETHICS (NCB), *Opinion on Migration and Health*, 2017, cit.: L. PALAZZANI, *Innovation in Scientific Research and Emerging Technologies. A Challenge to Ethics and Law*, cit.; i-CONSENT D1.4, *Ethical issues concerning informed consent in translational/clinical research and vaccination*, cit.

[33] E.S. DOVE, S.E. KELLY, F. LUCIVERO, B. PRAINSACK, ET AL., *Beyond individualism: Is there a place for relational autonomy in clinical practice and research?*, in *Clinical Ethics*, 12 (3), 2017, pp. 150-165.

[34] CIOMS, *Drug development research in Resource-Limited Countries. How to succeed in implementation of Good Clinical Practice Guidelines. Draft report of the Joint CIOMS/WHO Working Group*, 2005, cit.; CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, Geneva, 2016, cit.; CIOMS, *International Ethical Guidelines for Epidemiological Studies*, 2009, cit.

[35] TRUST PROJECT, *Global Code of Conduct for Research in Resource-Poor Settings*, 2018, cit., in particular art. 21: **"**Lower educational standards, illiteracy or language barriers can never be an excuse for hiding information or providing it incompletely. Information must always be presented honestly and as clearly as possible. Plain language and a non-patronising style in the appropriate local languages should be adopted in communication with research participants who may have difficulties comprehending the research process and requirements".

[36] P. MARSHALL*, Ethical challenges in study design and informed consent for health research in resource-poor settings*, cit.

lish but discuss it in the local language[37]; pre-testing consent forms with individuals from the study population provides useful direction concerning the need to revise consent forms so that they are meaningful and understandable for study participants[38]. Third, researchers have historically used strategies such as storytelling, performance or theatre, and more recently have looked into using visual tools, such as creating small video clips where a community member explains the research and the consent process in their mother tongue[39].

Community engagement is a recognized ethical requirement[40] and it is also a crucial element of an interculturally sensitive informed consent. Potential cultural sensitivities should be explored in advance of biomedical research with local communities, research participants and local researchers to avoid violating customary practices[41], often through the contribution of the local trusted "spokesperson", a person who not only can translate but also help to understand cultural values and perceptions[42], such as a contact person between the community and the research team[43]. Consultation with community members[44], in particular on how to work with the community, e.g. providing a forum for discussing and addressing issues arising from participants and community representatives[45], alongside an ongoing "dialogue" between researchers and the community about the proposed study and

[37] H3Africa Working Group on Ethics and Regulatory Issues for the Human Heredity and Health in Africa (H3Africa) Consortium, *Guidelines for informed consent* (2017), available at https://h3africa.org/wp-content/uploads/2018/05/H3A%202017%20Revised%20IC%20guideline%20for%20SC%2020_10_2017.pdf, last visited March 25th, 2019.

[38] P. Marshall, *Ethical challenges in study design and informed consent for health research in resource-poor settings*, cit.

[39] K. Chatfield et Al., *Research with, not about, communities – Ethical guidance towards empowerment in collaborative research, a report for the TRUST project*, 2018, cit.

[40] See CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, cit., guideline 7, *Community engagement*; see also EGE, *Ethical aspects of clinical research in developing countries. Opinion n. 17*, 2003, cit., n. 2.4, Partnership; CIOMS, *International Ethical Guidelines for Epidemiological Studies*, 2009, cit., guideline 4, *Individual informed consent*, par. on *Cultural considerations, consultation with community members* et seq.; J.J.M. van Delden, R. van der Graaf, *Revised CIOMS International Ethical Guidelines for Health-Related Research Involving Humans*, cit.; K. Chatfield et al., *Research with, not about, communities – Ethical guidance towards empowerment in collaborative research, a report for the TRUST project*, 2018, cit.

[41] See Trust Project, *Global Code of Conduct for Research in Resource-Poor Settings*, 2018, cit., art. 8, "Respect".

[42] A. Halkoaho et al., *Cultural aspects related to informed consent in health research: A systematic review*, in *Nursing Ethics* 23(6), 2016, pp. 698-712; J. Hughson et al., *A review of approaches to improve participation of culturally and linguistically diverse populations in clinical trials*, in *Trials*, 17 (2016), 263; K. Chatfield et al., *Research with, not about, communities – Ethical guidance towards empowerment in collaborative research, a report for the TRUST project*, 2018, cit.; V. Angwenyi, *Complex realities: community engagement for a paediatric randomized controlled malaria vaccine trial in Kilifi*, Kenya, cit.; L. Condon et al., *Engaging Gypsy, Roma, and Traveller Communities in Research: Maximizing Opportunities and Overcoming Challenges*, cit.

[43] K. Chatfield et al., *Research with, not about, communities – Ethical guidance towards empowerment in collaborative research, a report for the TRUST project*, 2018, cit.

[44] See CIOMS, *International Ethical Guidelines for Epidemiological Studies*, 2009, cit., guideline 4, *Individual informed consen*t, par. on *Consultation with community members*; CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, cit.; P. Marshall, *Ethical challenges in study design and informed consent for health research in resource-poor settings*, cit.; L. Palazzani, *Innovation in Scientific Research and Emerging Technologies. A Challenge to Ethics and Law*, Cham (Switzerland), 2019, cit.

[45] V. Angwenyi, *Complex realities: community engagement for a paediatric randomized controlled malaria vaccine trial in Kilifi*, Kenya, cit.

its potential implications, or a more structured consultation taking into account the concerns of a community or a socially identifiable group[46] are recommended advices.

3. Interaction between gender, culture and education in cross-cultural communication

3.1. Gender and health literacy

There are some specific barriers related to the interaction between gender and multicultural issues in cross-cultural communication, within geographically different research settings. In this regard, a study conducted by Killawi *et al* in the Arabian Gulf Region (particularly in the high-density multicultural setting of Qatar) describes how prospective research participants perceive their potential participation. As for the participant recruitment procedure, cultural norms in Qatar require that interactions between men and women occur in public space except for purely medical reasons or necessity depending on the task.

The mostly Muslim and all-female research assistants involved in the study believed it would be culturally inappropriate for them to be in a private room with a man. In addition, more women in the Arabic language group declined participation compared to any other language group (they felt compelled to discuss with a family member whether to participate and were concerned about recorded interviews for privacy reasons).

The study devises some best practices relating to a gender and culturally-tailored approach to recruitment procedures: culturally-competent and language concordant female research assistants were involved in research procedures to avoid neglecting cultural patterns regarding gender interactions; findings show that relying on male research assistants to recruit female subjects is more likely to clash with cultural sensitivities about gender interactions in the geographical context under consideration and, thus, lead to a negative impact on the research, compared to female research assistants recruiting male individuals. Recruitment took place in "gender specific waiting areas"[47] with female research assistants wearing white research coats to convey their official status and mitigate cultural patterns of gender separation. In this case, consent procedures were tailored to local cultural and social patterns; this empirical study has led to the conclusion that taking into account cultural influences results in an increased participation rate[48].

Moreover, research ethics guidelines and scientific studies identify a number of recommended practices taking into account women's health literacy: emphasis is placed on the need to improve the understanding of information: "[…] providing information through health workers (and particularly female health workers when the research will involve women), rather than physicians so that participants feel more at their ease to discuss and ask questions". Another key element concerns "providing information about a research project in various ways that are appropriate to the community (i.e. in

[46] See CIOMS, *International Ethical Guidelines for Epidemiological Studies*, 2009, cit., *Commentary on Guideline 4, Individual Informed Consen*t, par. on *Consultation with community members*.

[47] A. KILLAWI ET AL., *Procedures of recruiting, obtaining informed consent, and compensating research participants in Qatar: findings from a qualitative investigation*, in *BMC Medical Ethics*, 15, 2014, p. 9.

[48] A. KILLAWI ET AL., *Procedures of recruiting, obtaining informed consent, and compensating research participants in Qatar: findings from a qualitative investigation*, cit.

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parts of Africa, information has been supplied on audio or video tape, on the radio and through ballad singers); in some communities, particular care will need to be taken to ensure that the methods of providing information and aiding understanding which are adopted will ensure that the information reaches all members of the community. For example, if public meetings are used, it must be borne in mind that young women may feel unable to ask questions during such a meeting"[49].

Other recommended practices focus on the importance of increasing understanding of cervical cancer perceptions and beliefs: in this regard, Mwaka *et al.* explore community perceptions, beliefs and knowledge, in Northern Uganda, about local names, causes, symptoms, course, treatment, and prognosis of cervical cancer in order to inform targeted interventions to promote early help-seeking. The study suggests that "awareness campaigns to promote early help-seeking for cervical cancer symptoms need to be culturally-sensitive and context-specific; and include messages on symptoms, risk factors, course, treatment and prognoses"[50].

In order to improve awareness of Muslim women health beliefs, a study by Walton *et al*. stresses that although Muslim women prefer to make autonomous decisions concerning their health and not delegate this role to male family members, ultimately they believe it is important to consult with them during the decision-making process. Muslim women think that interacting with a female health care provider is imperative. In particular, they are inclined to access medical and rehabilitation services if provided by a female, but not when provided by a male health care provider; they are equally persuaded that relying on prayer, recitation of Quran, fasting, charity could be beneficial to their health, and are at ease with the use of physical touch in medicine and rehabilitation evaluation and treatment, if the care provider is female[51].

In the context of best practices aimed at improving informed consent of women in an intercultural setting, a number of studies point out the usefulness of multimedia tools for facilitating the communication process: Muhammed Olanrewaju Afolabi *et al.*, in this respect, assessed the effectiveness of a multimedia informed consent tool for adults participating in a clinical trial in the Gambia. A computerized, audio questionnaire was used to assess participants' comprehension of informed consent. This was done immediately after consent had been obtained and at subsequent follow-up visits (days 7, 14, 21 and 28). The acceptability and ease of use of the multimedia tool were tested in focus groups. Poorer comprehension was independently associated with female sex. A multimedia informed consent tool significantly improved comprehension and retention of consent information by research participants with low levels of literacy: research concepts that are known to be difficult to understand were clearly illustrated using video recordings and animations and explained by sound tracks in three local languages[52].

In a study on HIV research in South Africa, Staunton *et al.* highlight that obtaining consent in low-and middle-income countries can be challenging, and they identify ethical issues in developing an educa-

[49] NUFFIELD COUNCIL ON BIOETHICS, *The ethics of research related to healthcare in developing countries*, 2002, p. 11.
[50] A.D. MWAKA ET AL., *Understanding cervical cancer: an exploration of lay perceptions, beliefs and knowledge about cervical cancer among the Acholi in northern Uganda*, in *BMC Women's Health*,14:84, 2014.
[51] L.M. WALTON ET AL., *Health Beliefs of Muslim Women and Implications for Health Care Providers: Exploratory Study on the Health Beliefs of Muslim Women*, in *Online Journal of Health Ethics*, vol. 10, 2, 2014.
[52] M.O. AFOLABI ET AL., *A multimedia consent tool for research participants in the Gambia: a randomized controlled trial,* in Bulletin World Health Organization, 93(5), 2015, pp. 320–328A.

tional video to empower potential participants during consent processes. This tool has been prepared taking into account gender differences and some critical points emerged. Low levels of education, complexity of science and research processes, confusion about basic elements of research, and socio-economic conditions that make access to medical care difficult have led to concerns about the adequacy of the consent process. Evidence showed the importance of early community engagement in educating potential research participants and promoting community acceptance of research. This study reported that a 15-minute educational video entitled 'I have a dream: a world without HIV' was developed to educate and empower potential research participants to make informed choices during consent processes in future HIV cure clinical trials. The decision to include two women as the HIV-positive actors, instead of a male and female actor, turned out to be problematic as it may fuel misconceptions that women are carriers of the disease. In South Africa, women are generally in charge of the care of a child, and thus the caregiver needed to be female; equally, issues such as rape and female contraceptive methods, also required a female actor. This video prototype could be used in research targeted at different populations, and coupled with a variety of different media[53].

3.2. Culturally-sensitive communication for the inclusion of pregnant women in clinical trials

Cultural issues and the scientific knowledge gap between researchers and participants, directly affecting the latter's capacity to clearly understand the underlying risks related to their specific health condition should be carefully weighed, especially in sensitive circumstances, such as those in which the involvement of pregnant women in clinical research is envisaged.

In this context, Frew *et al.* 2014 provide a number of interesting culturally-sensitive strategies for the inclusion of pregnant women in clinical research: community outreach to advise providers about studies: this aspect is key to helping women overcome unease and distrust of the research (the most common reason for women's unwillingness to enrol in studies was identified with a preference for protocols that enabled them to follow-up on study results with their clinician); face-to-face interactions with health providers; health staff education and message training, along with study promotion via clinic media, print material, and interpersonal communication, in order to enhance patient receptivity to recruitment; conducting research within a community space or offering home visits: low-income women may not have reliable access to research study sites, particularly if they rely on a friend or family member for transportation, or use of public transportation; explaining the objective of clinical trials for testing drugs for pregnant women in hospitals and obstetric offices has been successful in identifying and enrolling eligible pregnant women for immunization trials; in general, visits to community groups in their geographic area; giving the possibility to discuss with friends and family members; community engagement strategies, including focus groups among pregnant women to identify important barriers and facilitators to research participation, relying on targeted messages and culturally-sensitive information materials adapted to gender needs and preferences, as well as community-based participatory research methods; accommodation of time constraints of pregnant women by taking advantage of mobile technology and the prevalence of cellular phone usage. For

[53] C. STAUNTON ET AL., *Ethical challenges in developing an educational video to empower potential participants during consent processes in HIV cure research in South Africa*, in *Journal of Virus Eradication*, 4(2), 2018, pp. 99–102.

example, the Text4baby (T4B) program, launched in 2011, attempted to improve health behaviour and perceptions among pregnant women by employing a text messaging program. T4B successfully changed attitudes toward pregnant women's health behaviour and thus it is recommended as method to alter perceptions of clinical trial practicality and overall potential benefits to their health. Disseminating messages via cellular phone usage allows investigators to educate eligible participants without taking additional time out of pregnant women's schedules. Education via mobile technology that has promoted significant changes in health behaviours and perceptions may also help providers restrained by clinical duties to reach eligible patients and use a similar program to educate them on available studies. Social networking sites have been employed as an effective method of increasing recruitment rates among pregnant women.

Culturally appropriate messages and research tailored to the need of prospective participants are among the most effective strategies contributing to successful retention of pregnant women in research trials. These findings further highlight the importance of recruitment methodology that is carefully tailored to interests and needs of pregnant women[54].

3.3. The role of the male partner in the informed consent process

There is broad consensus in international and European guidelines on the fact that in no case permission by the woman's partner may replace the individual informed consent of the woman herself, since this would result in a violation of the principle of respect for the person. However, if the woman wishes to consult with husband or partner before deciding to enrol in research, that is deemed to be not only ethically permissible, but in some contexts highly desirable[55]. In addition, different cultures may also have different views concerning privacy and personal data, which can impinge on the acceptability of certain aspects of research protocols, especially with regard to data collection, as well as the data subject's right of access and right to object[56].

The NBC stressed the fact that in some cultural contexts women tend to delegate decisions concerning their health to a partner, a male family member or the family group. In this perspective, the Italian Committee for Bioethics, proposes an interpretation of the concept of autonomy in terms of "relational autonomy", which may be better tailored to an intercultural approach aiming at accommodating the value of the community dimension in certain cultural settings and respect for the person[57].

In the context of research participation, women living in a social context of patriarchal authority, having a low literacy level, may adopt a passive behaviour with regard to enrolment procedures or not seek interaction with researchers in case of insufficient understanding of the study evolution. There-

[54] P.M. Frew Et Al., *Recruitment and Retention of Pregnant Women Into Clinical Research Trials: An Overview of Challenges, Facilitators, and Best Practices*, in *Clinical Infectious Diseases*, 59 (7), 2014, pp. S400–S407; Martinez Perez et Al.,*'Researchers have love for life': opportunities and barriers to engage pregnant women in malaria research in post-Ebola Liberia*, in *Malaria Journal*, 17(1) 2018, p. 132.

[55] Royal College Of Physicians, *Guidelines on the practice of ethics committees in medical research with human participants*, 2007.

[56] Ege, *Ethical aspects of clinical research in developing countries. Opinion n. 17*, 2003, available at https://publications.europa.eu/en/publication-detail/-/publication/6339dcbf-c156-4e7f-9e43-9928acf82118/language-en/format-PDF/source-77404483, p. 13.

[57] Italian Committee for Bioethics (nbc), *Opinion on Migration and Health*, 2017, p. 38.

fore, as stressed by the UK Royal College of Physicians, "research ethics committees should exercise special care in examining the proposed consent process to ensure adequate time and a proper environment in which a decision to participate can be made"[58].

Involving particularly vulnerable women (for instance those living in poor socio-economic conditions) in clinical research should be carefully assessed, in order to avoid, on one side, any form of discrimination by excluding specific population groups from participation, which can directly (as individuals) or indirectly (as population group) benefit them; and, on the other, to prevent any form of coercion or undue inducement.

The role of male family members or partners may have a different impact on the woman's decision to participate in clinical research in diverse cultural groups. Looking into a number of geographical and cultural perspectives, the Nuffield Council on Bioethics highlights some considerations about women decision- making: in some South Asian regions, **"**women may not always be able to express personal opinions on even minor matters, let alone the issue of whether they would like to take part in research. The notion that individuals are free to make their own decisions will therefore be less familiar to such women**"**[59]; in China, women are usually not expected to obtain the permission of men or elders before deciding to participate in research. However, before consent can be sought, **"**a visiting research team's proposals will need to be discussed in an open manner through the offices of the village cadre committees**"**[60]; in many parts of Africa, women, especially in non-Muslim societies, have developed a more assertive position with regard to healthcare, often aided by mission hospitals, clinics and health focused non-governmental organisations. "As cultures are not fixed, researchers may need to find means of fostering discussion about what is required by cultural norms in a particular context. For example, research in South Africa has shown that even within a culture with strong beliefs about the importance of the community, many women favour the approach of requiring individual consent to research". In addition, in some areas of Uganda with traditional social and cultural values, men (husband/father as the head of the family) are expected to decide on all matters, especially sensitive ones affecting family members. Therefore, family members who do not submit to such decisions may face serious consequences including domestic violence and/or divorce. In this context, **"**women and children will tend not to participate in a study unless permission has been granted by the head of the household**"**[61]; in Latin America, unlike the cultural contexts mentioned above, community consent or other types of group consent are not common practice. Although collective information can be provided to rural communities or ethnic minorities, such as indigenous populations, consent by individual participants is accepted[62].

In this regard, the US National Bioethics Advisory Commission recommends that **"**researchers should use the same procedures in the informed consent process for women and men. However, ethics review committees may accept a consent process in which a woman's individual consent to participate in research is supplemented by permission from a man if all of the following conditions are met: a) it

[58] Royal College of Physicians, *Guidelines on the practice of ethics committees in medical research with human participants*, cit.

[59] Nuffield Council on Bioethics, *The ethics of research related to healthcare in developing countries*, cit.

[60] Nuffield Council on Bioethics, *The ethics of research related to healthcare in developing countries*, cit.

[61] Nuffield Council On Bioethics, *The ethics of research related to healthcare in developing countries*, cit.

[62] Nuffield Council On Bioethics, *The ethics of research related to healthcare in developing countries*, cit.

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would be impossible to conduct the research without obtaining such supplemental permission; and b) failure to conduct this research could deny its potential benefits to women in the host country; and c) measures to respect the woman's autonomy to consent to research are undertaken to the greatest extent possible. In no case may a competent adult woman be enrolled in research solely upon the consent of another person; her individual consent is always required"[63].

3.4. Best practices on culturally-tailored health communication programs with a gender perspective

The *Gender guide for health communication programs* issued by the US Center for Communications Programs (2003) points out the importance of including gender concerns in health communication initiatives, aimed at making health messages more effective and foster awareness of the necessity of equity in terms of gender needs. A gender perspective in communication should take into account ways in which gender influences health needs and concerns, different roles and interests of women and men, as well as the reception of health messages. Seeking feedbacks of effective communication strategies is highly recommended, also by conducting evaluations in different cultural communities. It is critical to speak to women and men separately to obtain reliable gender-informed perspectives.
In this context, it is possible to identify a set of culturally-sensitive communication strategies with a gender perspective (i.e. "the ways in which gender influences health needs and concerns, the reception of health messages, and access to and control over health communication interventions"[64]): health communication programs should take into account different needs, roles, and interests of women and men; spousal communication and power dynamics between men and women; decision-making processes; social and cultural constraints and opportunities; communication initiatives should assess potential positive and negative program impacts and communication capacity (e.g. access to media for women and men and their media habits: devising which communication channels, radio, tv, print, talks, community meetings, are used by women/men for health information and how this differs according to age and education levels); communication strategies should ensure that services, supplies, and practices of chosen media do not reinforce gender stereotypes; pretesting and re-testing messages, concepts, and intended program formats with women and men separately to determine what works well for women and what works well for men. These materials should be tailored to the different cultural groups they are addressed to.
In the context of a cultural adaptation of information, Brown *et al.* reported that ethnic-specific information about health risk associated with recipients' health condition increased recruitment of African American women into clinical trials. They provided evidence that "many patients and family members misunderstood trial information and that many felt that a question prompt lists and decision aids would assist in decision-making". In addition, they suggested that the best strategies to reduce enrolment barriers and retain participants are associated with the ability to keep constant contact with participants. Moreover, being respectful and showing a caring attitude are the important

[63] US NATIONAL BIOETHICS ADVISORY COMMISSION, *Ethical and Policy Issues in Research Involving Human Participants*, 2001, p. 4.
[64] JOHN HOPKINS UNIVERSITY CENTER FOR COMMUNICATION PROGRAMS, *The Gender Guide for Health Communication Programs*, 2003.

factors in this population. The authors equally stressed that findings may not be specific to African American population but can apply to other ethnic groups[65].

Among the innovative strategies aimed at the inclusion of women from diverse cultural backgrounds in clinical trials, Jones *et al.* illustrated a *Facebook* advertising of a clinical trial with African American women and provide a practical guide to create and publish a Facebook ad for a target population. This approach can be adapted to different study populations in diverse cultural settings. Although online recruitment lacks face-to-face contact, there is evidence that for many, such contact did not deter recruitment. Advertising for enrolment in clinical trials via social networking sites, specifically Facebook, has led to encouraging results in expanding geographic reach while still targeting a population and maintaining confidentiality. A broad representative distribution, including those less accessible via traditional venue sampling due to stigma may be reached online for participation in clinical trials[66].

4. Strategies to overcome communication barriers between researchers and research participants

4.1 Cultural competence training for researchers working with subjects from diverse cultural and religious backgrounds

For an adequate informed consent process, personal interaction between subjects involved in clinical trials and researchers is essential. The informed consent process involves an interactive conversation between the research participant and the research staff, during the whole process.

The research staff should be educated to deliver the information in an efficient and responsive manner. With training, research staff may become more confident in the accuracy of their knowledge and improve their interaction skills. CTTI Recommendations stressed the need that research staff obtaining consent should be trained to do so. An informed consent training program should aim to improve knowledge and communication skills of researchers[67].

Researchers should improve their ability to communicate effectively with diverse patients, especially when they are people from diverse cultural and religious backgrounds. In these cases, communication can be more challenging. It is therefore recommended that researchers develop cultural competence, namely awareness of cultural influences on patients' health beliefs and behaviours.

Cultural competence of the research team is recognised as very important[68]. More specifically, cultural competence training for researchers would guarantee an effective communication and interaction with participants from diverse cultural and religious backgrounds. The development of cultural

[65] R.F. Brown et al., *Perceptions of participation in a phase I, II, or III clinical trial among African American patients with cancer: what do refusers say?*, in J Oncol Pract. 9 (6), 2013, pp. 287-93.

[66] R. Jones, L.J. Lacroix, *Facebook Advertising to Recruit Young, Urban Women into an HIV Prevention Clinical Trial,* in *AIDS and Behavior*, 21(11), 2017, pp. 3141-3153.

[67] Clinical Trials Transformation Initiative, *CTTI Recommendations: Optimizing Mobile Clinical Trials by Engaging Patients and Sites*, Feb. 21, 2019, available at https://www.ctti-clinicaltrials.org/projects/engaging-patients-and-sites, last visited March 1st, 2019.

[68] M. Truong, Y. Paradies, N. Priest. *Interventions to improve cultural competency in healthcare: a systematic review of reviews*, in *BMC health services research*, 2014, 14:99.

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competence needs to be seen as an ongoing process. Strategies to develop cultural competence of researchers in order to increase the recruitment of participants who are unable communicate fully due to cultural barriers should be promoted. These strategies should include the following aspects. Firstly, an adequate education of researchers should be promoted: an increase in the intercultural skills of the researchers is recommended, in order for them to be able to interact appropriately with participants from diverse cultures, in the perspective of intercultural communication. It could be useful to devote adequate consideration, within university training paths, to studies focusing on the therapeutic relationship in an intercultural perspective (the so-called transcultural medicine).
Finally, it could be important to guarantee a continuity of the research team. In fact, when the researcher who interacts with each participant is the same through the different phases of a clinical trial, this helps build a bond of trust between researchers and prospective participants and maintain consistency in the conveyance of information;
These strategies aim at strengthening an intercultural sensitive approach to communication among researchers and potential participants in clinical trials and may contribute to improve participation of people from diverse cultural backgrounds in research. In this sense, open and understandable communication between researchers and participants during the whole research process could help creating trust in relationship and maintaining consistency in the information, thus, overcoming one of the main barriers in communication.

4.2. Innovative strategies to improve the informed consent process in an intercultural setting

Advances in technology enable novel communication approaches, allowing researchers to adapt the informed consent process to persons of diverse health literacy of all backgrounds[69]. Apps, tablets, video, interactive computers, robots, personal digital assistants, smartphones, and wearable technology, could help to modernize and improve methods for obtain informed consent. The adoption of digital tools within the IC process could facilitate and develop practices that are more culturally appropriate and that reflect the values, customs, and level of exposure of local communities to research[70].
At international level, the guidelines include an ethical analysis of the use of digital technologies in healthcare in general. The Report of the International Bioethics Committee of UNESCO (IBC) on Big Data and Health (2017) stressed the importance and problems about informed consent given electronically (informatic consent), specifying that electronic means in clinical research may be efficient and effective as long as there are safeguards implemented to ensure that the participants' autonomy is respected[71]. The CIOMS International Ethical Guidelines for Epidemiological Studies (2009), focus,

[69] J. KAYE, E.A. WHITLEY, D. LUND, M. MORRISON, H. TEARE, K. MELHAM, *Dynamic consent: a patient interface for twenty-first century research networks*, in *European Journal of Human Genetics*, 2015, 23(2), pp. 141-146; E. M. MESLIN, S.A. ALPERT, A.E. CARROLL, J.D. ODELL, W.M. TIERNEY, P.H. SCHWARTZ, *Giving patients granular control of personal health information: using an ethics 'Points to Consider' to inform informatics system designers*, in *International Journal of Medical Informatics*, 2013, 82 (12), pp. 1136-1143.
[70] A.C. JONES, E. SCANLON, G. CLOUGH, *Mobile learning: Two case studies of supporting inquiry learning in informal and semiformal settings*, in *Computers & Education*, 2013, 1-22.
[71] UNESCO INTERNATIONAL BIOETHICS COMMITTEE (IBC), *Report of the IBC on Big Data and Health*, 2017, available at https://unesdoc.unesco.org/ark:/48223/pf0000248724, last visited March 1st, 2019.

in the Guideline n° 6, on responsibility of the investigator for ensuring the adequacy of informed consent from each subject[72]. When subjects are enrolled in studies by mail or electronic means (e.g., e-mail, Internet, etc.), difficulties may arise in fulfilling investigators' duties to ascertain that subjects adequately understand relevant facts. Potential subjects enrolled in these ways should therefore be given a means (such as a toll-free phone number or email address) to enable them to pose questions to, and receive answers from, the research team concerning the study.

Tools to provide information are the following:

a) videos: the value of audio-visual interventions as a tool for helping to improve the informed consent process for people considering participating in clinical trials should be take into account. Audio-visual presentations can ensure the clear delivery of information that is complete, consistent and unbiased, to supplement or reduce staff time spent in seeking informed consent. A study of the feasibility of using multimedia technology during the informed consent process for clinical research reported that the use of the video made information more understandable[73];

b) animations: a study on 58 focus groups of African Americans, Latinos, Native Hawaiians, and Filipinos in Los Angeles/Hawaii demonstrated that via animation improved the communicating information about health research[74]. After viewing the video, participants appeared to be able to identify gaps in knowledge about research and to express an increased desire to seek information to address these gaps. In addition, the findings also suggest that animations may be augmented when accompanied by a community facilitator or a family member. The advantage of the animations is that are easier to be customized according to the subject's characteristics;

c) interactive tools: in general, interactive tools have a better impact in comprehension of information and long-term memory then non-interactive tools, so a combination of interactivity and animation could be a good solution to design innovative digital-based strategies[75].

Digital innovation and interactivity can indeed play a central role for the success of these strategies. Scientific evidence highlights the positive impact of a strategy blending personal relationship and innovative, video-based and digital tools[76].

A scientific study focused on a self-administered, web-based survey using an experimental between-group design to compare the effects of four informational aids on respondents' understanding of core aspects of research[77]. The aim was to verify what methods could improve informed consent in clinical research settings. Multimedia informational aids assessed were the following: animated videos (audio, character-driven); slideshows with voice-over (audio, not character-driven); comics (no audio, character-driven); text (no audio, not character-driven). Findings showed that knowledge

[72] CIOMS, *International Ethical Guidelines for Epidemiological Studies*, 2009, cit.

[73] A. SYNNOT, R. RYAN, M. PRICTOR, D. FETHERSTONHAUGH, B. PARKER, *Audio-visual presentation of information for informed consent for participation in clinical trials*, in *Cochrane Data base of Systematic Reviews*, 2014, 1-40.

[74] G. SHEBA ET AL., *Using Animation as an Information Tool to Advance Health Research Literacy among Minority Participants*, in *AMIA Annual Symposium Proceedings*, 2013, e16-e28.

[75] R.L. OWNBY ET AL., *Health literacy predicts participant understanding of orally presented informed consent information*, in *Clinical Research Trials*, 1 (1), 2015, pp. 15–19.

[76] A.R. TAIT, T. VOEPEL-LEWIS, *Digital multimedia: a new approach for informed consent?*, in Journal of American Medical Association, 2015, 463.

[77] S.A. KRAFT, *A randomized study of multimedia informational aids for research on medical practices: Implications for informed consent*, in *Clinical Trials,* 2017, pp. 94-102.

scores were significantly higher for the two informational aids with an audio component (animated videos and slideshows with voice-over) than in the two without (comics and text). Consequently, using multimedia informational aids (especially if with audio approach) could help to bridge the knowledge deficit about research and guarantee an information tailored to persons of diverse health literacy levels and of all backgrounds[78].

In this regard, the Clinical Trials Transformation Initiative (CTTI) developed a Project, with the objective to identify barriers to communication of informed consent elements and develop recommendations for improving the informed consent[79]. Among these:

1) engaging patients and sites to drive adoption of mobile technology in clinical trial; engaging patients and sites in planning clinical trials using mobile technology, including protocol design, technology selection, and pilot testing, in order to enhance satisfaction and engagement, recruitment and trial feasibility. Patients' perspectives can be identified through advisory panels, surveys, focus groups, simulation exercises and other methods (a range of relevant perspectives should be represented, including appropriate and diverse racial and cultural backgrounds);
2) select mobile technologies based on requirements of the study and needs of the intended user population, starting with the aspect that the assessment is intended to measure (engage patients and sites in technology selection; conduct feasibility studies to ensure that study participants find the technologies easy to learn, simple and convenient to use, physically comfortable);
3) when planning a trial using mobile technologies, identify and conduct necessary pilot studies with sites and a representative patient population. Mobile technologies can change the way sites and participants interact during a trial (For example, mobile technology can reduce the need for in-person visits and facilitating participation in the trial).

Improving the consent process for culturally and linguistically diverse population participants has been the focus of several studies, which emphasized the importance of adopting a multimethodological approach, including the use of culturally and linguistically sensitive multimedia tools, to tailor the information process to the needs of subjects from diverse cultural and religious backgrounds in clinical research. Multimedia resources may have key roles to play in addressing health research literacy by explaining medical research, enabling researchers to assess comprehension through testing, and improving participant comprehension of consent forms and procedures. Furthermore, multimedia tools could be used by researchers, who do not necessarily speak the language of the research participants[80].

Clinical trial participants in sub-Saharan Africa often have limited understanding of the study information provided during the informed consent process. In countries such as the Gambia, where local

[78] In the UK, the Guidance of Health Research Authority (HRA), with particular regard to clinical trials, stressed the importance of the use of media or non - text - based approaches (videos, cartoons, animations, info graphic cards, flipcharts, brochures and audio). These methods may be used as patient- friendly introductions to complement, or replace, the traditional paper information sheet. See THE HEALTH RESEARCH AUTHORITY, *Guidance relating to the inclusion or exclusion of participants in research who may have difficulties in adequate understanding of English*, 2018.

[79] CLINICAL TRIALS TRANSFORMATION INITIATIVE, *CTTI Recommendations: Optimizing Mobile Clinical Trials by Engaging Patients and Sites*, cit.

[80] J. HUGHSON ET AL., *A review of approaches to improve participation of culturally and linguistically diverse populations in clinical trials*, in *Trials*, 2016, 17:263.

languages have no standard written form, translating documents into the local language and back translating into the national language is impractical[81]. In particular, illiterate participants may not understand research concepts and this fact could undermine their ability to give truly and effective informed consent.

A study on effectiveness of the multimedia tool in malaria treatment trial in the Gambia confirmed that use of a multimedia informed consent tool results in significantly better understanding of clinical trial information than the current standard method for obtaining consent. In the scientific study, the multimedia tool was tailored to the cultural and linguistic diversity of the Gambian population: the visual and verbal information presented through the DVD resulted clear and easy to understand in an area of the Gambia with low levels of literacy.

4.3. Ethical challenges related to the use of ICT and social media in clinical research: e-Consent in an intercultural setting

The expression 'e-Consent' refers to the use of any electronic media (such as text, graphics, audio, video, podcasts or websites) to convey information related to the study and to seek informed consent via an electronic device (such as smartphone, tablet or computer). These electronic methods are adopted by researchers either to supplement or substitute the traditional paper-based approach. E-consent may increase understanding of the study, particularly for people with a low educational level or limited literacy.

Most studies have shown that participants' recall of key facts about a study is better with the use of e-consent with these interactive features than with paper forms[82]. However, there are also challenges regarding electronic consent for researchers. First of all, when the consent documents are provided by electronic methods there is the problem to verify the participant's identity. Additionally, there is the problem of the high initial expense for infrastructure and technology to manage online documents and establish systems to validate electronic consent.

The use of multimedia informational aids in clinical research shows many advantages.

Ensuring participant comprehension continues to be a challenge in e-Consent. A study focused on assessment of a convenience sample of participant reaction to the e-Consent implementation (within the Parkinson mPower mobile study) using a mixed methods approach[83].

The starting point was that to fully capitalize on mobile technology we must develop companion self-administered electronic informed consent (e-Consent) processes. Incorporating novel informed consent approaches on a target study population diverse in terms of ethnicity, primary language and health literacy, demonstrating that the use of the electronic consent (e-Consent) not only increases the opportunity to recruit patients culturally isolated, but also has the potential to increase the trust.

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[81] M.O. Afolabi et al., *A multimedia consent tool for research participants in the Gambia: a randomized controlled trial,* cit., p. 320.

[82] J. Kaye, E.A.Whitley, D. Lund, M. Morrison, H. Teare, K. Melham, *Dynamic consent: a patient interface for twenty-first century research networks*, cit., 141-6; C.M. Simon, D.W. Klein, H.A. Schartz, *Interactive multimedia consent for biobanking: a randomized trial*, in *Genetics in Medicine*, 18 (1), 2016, pp. 57-64.

[83] M. Doerr, A. Maguire Truong, B.M. Bot, J. Wilbanks, C. Suver, L.M. Mangravite, *Formative evaluation of participant experience with mobile eConsent in the App-Mediated Parkinson mPower Study: a Mixed Methods Study, in Journal of Medical Internet Research Mhealth Uhealth*, 5 (2), 2016, pp. 42-47.

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A study underlines the advantages of use of technology in clinical trials[84]:

a) communication: technology tools improve communications not just with study staff, but also with patients and communities.
b) recruitment: using apps and social media could increase the number of participants contacted and enrolled.
c) retention: mobile phones/devices, apps, and social media offer the opportunity to connect with participants more often and potentially improve their involvement and retention. Smartphones, apps, and wearable body sensors can allow for large quantities of data to be collected automatically and not require face-to-face interactions with researchers.
d) e-technology-based interventions can reduce resource requirements related to staff training and ongoing supervision, maintain consistent delivery of an intervention.
e) data collection: use of registries can improve targeted recruitment and make standard clinical data available in real-time for study outcome purposes. Digitized forms have been shown to improve data quality.

The use of social media in research consent may improve the quality of the consent process by overcoming awareness issues about trials and in particular low understanding of the concept of research. Furthermore, the use of these methods may improve comprehension issues associated with medical and legal jargon. The influence of ICT and the Internet including social media was an important factor in how healthcare services in Thailand are being offered and practiced. In Thailand, the use of social media for Thai healthcare professionals is emphasized on Facebook and LINE Chat applications. Thailand has achieved an elevated level of access to e-health services and use of ICT[85]. The use of social media in research consent allows research participants can open up online dialogue and interaction with professionals and exchange information during the process from anywhere and at any time[86].

App-based research has the advantage that all or most of the research study can be conducted through the smartphone, from obtaining informed consent to collecting data[87]. Conducting health research and obtaining informed consent on smartphones raise several unique challenges and limitations. The most important limitation is that there is no face-to-face confirmation of identity. Another challenge with respect to app-based research is data security and privacy.

Despite multimedia tools in clinical research have certainly important advantages, some ethical challenges to the use of digital technologies in informed consent remain.

a) First of all, Information Technologies could involve risks related to the processing and protection of privacy and personal data and misuse of these. A fundamental challenge lies in ensuring that patient data remain confidential and secure in order to build trust in the use of ICT[88].

[84] C. ROSA ET AL., *Using e-technologies in clinical trials,* in *Contemporary Clinical Trials,* 45, 2015, pp. 41-54.
[85] S. JANTAVONGSO, *Ethics, social media and e-health in Thailand,* in *Journal of the Thai Medical Informatics Association*, 1, 2015, pp. 25-37.
[86] D. O'CONNOR, *The apomediated world: regulating research when social media has changed research*, in *The Journal of Law, Medicine & Ethics*, 41 (2), 2013, pp. 470-83.
[87] C. GRADY, *The changing face of informed consent*, in *The New England Journal of Medicine*, 2017, pp. 856-867.
[88] EGE, *The ethical implications of new health technologies and citizen participation*. *Opinion n. 29*, 2015, available at https://publications.europa.eu/en/publication-detail/-/publication/e86c21fa-ef2f-11e5-8529-01aa75ed71a1/language-en/format-PDF/source-77404221.

b) The Guideline n° 23 (CIOMS, 2009) provides for that the investigator must ensure that an appropriate informed consent procedure is applied and that data confidentiality is maintained[89]. Subjects' privacy, confidentiality and security are at stake when data are conveyed to others electronically. In this regard, CIOMS, 2016, Guideline n. 22 (Use of data obtained from the online environment and digital tools in health related research) highlights the need for privacy protection in combination with technological capabilities[90]. When researchers use the online environment and digital tools to obtain data for health related research they should assess the privacy risks of their research, mitigate these risks as much as possible and describe the remaining risks in the research protocol. The development of regulations and codes to allow for the widespread, lawful, ethical and secure use of IT in research consent should be supported[91].

c) Furthermore, technology evolves constantly and available tools change continuously and keeping track of progress and available tools is challenging. Although smartphone use and familiarity with mobile technology are growing, they are certainly not evenly distributed across populations[92]. Scientific literature shows that in the African context, experiences with integrating ICT in action-oriented and cross-cultural communication projects have been developed later and more slowly than in high-income countries[93]. A digital divide means that unequal access to digital technologies as well as highly divergent levels of online literacy persist[94].

d) Even more of an ethical challenge is the inability of a part of population to participate in smartphone-based research studies because of issues related to access or cost of smartphones or data connectivity. Another issue concerns access to technologies. There is, today, a "digital divide" because of many factors, such as a socio-economic gap and the network coverage for the Internet in the area under consideration[95]. Equal access should be guaranteed, allowing everyone to acquire tools, knowledge, skills to use new information technologies, according to the principle of equality, equal opportunities and non-discrimination[96].

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[89] CIOMS, *International Ethical Guidelines for Epidemiological Studies*, 2009, available at https://cioms.ch/wp-content/uploads/2017/01/International_Ethical_Guidelines_LR.pdf

[90] CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, Geneva, 2016, https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf.

[91] C. TABER ET AL., *Improving the Quality of Informed Consent in Clinical Research with Information Technology*, in *Studies in Health Technology and Informatics*, 2016, pp. 135-142.

[92] C.R.N. GRADY, *The changing face of informed consent*, cit., p. 856.

[93] N. LARSEN, *ICT-based, cross-cultural communication: A methodological perspective,* in *International Journal of Education and Development using Information and Communication Technology* (IJEDICT), Vol. 10, Issue 1, 2014, pp. 107-120.

[94] EGE, *The ethical implications of new health technologies and citizen participation. Opinion n. 29*, 2015, cit.; ITALIAN COMMITTEE FOR BIOETHICS (NBC), *Opinion on Ethics, Health and New Information Technologies*, 2006.

[95] ITALIAN COMMITTEE FOR BIOETHICS (NBC), *Opinion on Mobile Health Apps: bioethical aspects*, 2015.

[96] ITALIAN COMMITTEE FOR BIOETHICS (NBC), *Opinion on Information and Communication Technologies and Big Data: Bioethical Issues*, 2016.

Informed Consent in Translational/Clinical Research. Ethical Issues According to International Guidelines

Margherita Daverio*

ABSTRACT: In translational research, the emphasis on advancements in scientific knowledge could prevail over the protection and the best interest of those who participate in the research; in particular, the duty of safety for human subjects could become far more challenging when moving from preclinical research to first-in-human trials, because of uncertainty, as preclinical research can fail to predict the risks for humans, and of risk, which could result in a greater than minimal risk, because of the acceleration of research in the shift from bench to bedside. The article discusses from an ethical point of view specific issues which informed consent in translational research should take into account.

KEYWORDS: Translational/clinical research; ethics; informed consent; safety; risk

SUMMARY: 1. Ethical issues in translational research – 2. Translational research: international documents and guidelines – 3. Informed consent in translational research – 4. Analogies and differences between innovative therapies and translational research – 5. The primary duty of safety for research participants in the leap from bench to bedside.

1. Ethical issues in translational research

In the medical field, the objective of translational research is, first of all, to transfer scientific knowledge from laboratory and pre-clinical research to clinical research on human subjects and to translate knowledge and advances generated in biomedical research into positive impacts on human health[1].

Basic research aims to generate knowledge but perhaps may not be immediately relevant for practical applications in patient care; translational/clinical research is described as research protocols involving patients. "The whole spectrum of research is essential, from basic, through translational to

* *Libera Università Maria Ss. Assunta (LUMSA), Roma.* E-mail*: m.daverio@lumsa.it*. *The article was subject to a double-blind peer review process.*

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[1] "A growing attention of the scientific community, of the governments and of the public opinion is today focused on the need of promoting translational research for health by initiatives instrumental for allowing the efficient transfer of the scientific discoveries into feasible preventive and therapeutic strategies for diseases at high socio-economic impact and relevance for the national health plans" (ISTITUTO SUPERIORE DI SANITÀ, *Infrastructures for Translational Research on Health and the Role of Istituto Superiore di Sanità*, November 2014, *Preface*, available at http://old.iss.it/binary/iatr/cont/Opuscolo_IR_2014.pdf, last visited 26/04/2019.

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patient-oriented research and back again. One part is ineffective without the other"[2]. For this reason, it is difficult to set clear boundaries between basic research and translational/clinical research. Nevertheless, the process of translation of knowledge can be defined as "the process of turning observations in the laboratory, clinic and community into interventions that improve the health of individuals and the public – from diagnostics and therapeutics to medical procedures and behavioural changes. Translational science is the field of investigation focused on the understanding the scientific and operational principles underlying each step of the translational process"[3]. *The European Society of Translational Medicine*[4] defines translational medicine as "an interdisciplinary branch of the biomedical field supported by three main pillars: benchside, bedside and the community. The goal of translational medicine is to combine disciplines, resources, expertise, and techniques within these pillars to promote enhancements in prevention, diagnosis, and therapies"[5]. In this perspective, translational research also entails the necessary steps to move from clinical research to medical practice and backwards (as a "two-way road", including the reverse path of transition from clinical practice to research), applying scientific findings to the routine healthcare. The concept of a "two-way road" or "two-way bridge" was developed when the overall scope of biomedical research – scientific knowledge – became closer to the help that clinical scientist engineers could give to health care through emerging technologies, taking advantage also of the increase of funding in this area[6].

The increasing development of translational research with human subjects[7] poses new challenges to the fulfilment of ethical standards for the protection of the human subjects involved, particularly in

[2] EUROPEAN SCIENCE FOUNDATION, *Implementation of Medical Research in Clinical Practice*, 2011, n. 5, available at http://archives.esf.org/fileadmin/Public_documents/Publications/spb45_ImplMedRes_ClinPract.pdf, last visited April 26th, 2019. This document explicitly deals with translational research and particularly with the difficulty to set clear boundaries between basic research and clinical research. In addition, in Annex 2 (Glossary), the document defines translational research as "the conversion of basic research advances into products that can be tested on humans" and in Annex 3 (Future Outlook: Emerging Innovative Approaches for Effective Integration of Medical Research in Clinical Practice) as "the multidisciplinary research necessary to advance preclinical or basic science findings to clinical and population health applications is often named as translation research".

[3] NATIONAL INSTITUTE OF HEALTH, *Translational Science Spectrum*, 2015, https://ncats.nih.gov/files/translation-factsheet.pdf, last visited April 8th, 2019.

[4] The European Society of Translational Medicine (EUSTM) is a global non-profit and neutral society whose principal objective is to enhance world-wide health care through the specific development and eventual clinical implementation and exploitation of Translational Medicine-based approaches, resources and expertise (The European Society for Translational Medicine, https://eutranslationalmedicine.org/, last visited April 8th, 2019).

[5] J. SHAHZAD ET. AL., *Translational Medicine definition by the European Society for Translational Medicine*, in New Horizons in Translational Medicine 2 (2015), p. 88.

[6] J. SHAHZAD ET. AL., *Translational Medicine definition by the European Society for Translational Medicine*, cit., p. 87. Also the NIH defined translational research as a two-way road "Although sometimes referred to as bench-to-bedside research, translational research really is a two-way street. Basic research scientists provide clinicians with new tools for use with patients, and clinical researchers make new observations about the nature and progression of disease that often stimulate basic investigations. Research on new outreach approaches and the cost-effectiveness and real-world feasibility of prevention and treatment strategies are important aspects of this endeavour, as they provide the feedback necessary to ensure the practicality of interventions" (THE NATIONAL INSTITUTE OF HEALTH, *Biennial Report of the Director*, Fiscal Years 2006-2007, available at https://report.nih.gov/biennialreport0607/, last visited April 8th, 2019).

[7] One of the reasons of the revision of CIOMS guidelines is the heightened emphasis, since 2002, on translational research, implementing relations between basic research advances and their use, in order to develop

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terms of risk. Every research which aims at innovation entails uncertainties and risks[8], which may be totally or partially unpredictable. Many risks related to translational research are common to the ones which are likely to be encountered in clinical research but there may be some specificities stemming from the goal to foster a fast translation of research results into innovative strategies for the prevention, diagnosis and treatment of diseases: the "leap from bench to bedside", peculiar to translational research, requires the duty to balance risks/benefits in a specific way. This expedited process, accelerated also by emerging technologies[9] needs greater precaution and caution to ensure that the timelines of procedures do not override the necessary protection and risk/benefit proportionality[10], which must be guaranteed to research participants.

In addition to the ethical issues in common with biomedical research in general – for example identifying principles and values of the research, the responsibilities of the various stakeholders, and an ethical oversight –, in the shift *from bench to bedside,* there are some specific problems related to the case of "first-in-man trials", where "the focus of research must always be on patients' interest. Therefore, the main problems are connected to the safety of those who participate in the research and to balance risks and benefits"[11]. The transfer *from bench to bedside* is a primary concern in translational research; however, researchers and physicians have a duty to protect the interests and welfare of research participants/patients, making sure that the safety, integrity and wellbeing of individuals prevails over all other scientific advancements or commercial interests[12]. In particular, when risks are too high compared to the benefits than can be reached (with a non-proportionality of

new therapies or medical procedures (see CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, *Preface*, available at https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf, last visited April 8th, 2019).

[8] In medical practice and medical research most of interventions involve risks and burdens, which must always be assessed before conducting a study involving humans (World Medical Association, *Declaration of Helsinki*, 1964 last version 2013, art. 16-17, available at https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/, last visited April 8th, 2019). Risks are ethically justified for the scientific and social value of research and should always be carefully balanced (see CIOMS, *Ethical Guidelines for Health-Related Research Involving Humans*, 2016, cit., Guideline 4, *Potential individual benefits and risks of research*, which recommends: " […] Before inviting potential participants to join a study, the researcher, sponsor and the research ethics committee must ensure that risks to participants are minimized and appropriately balanced in relation to the prospect of potential individual benefit and the social and scientific value of the research".

[9] For an ethical overview of emerging technologies in scientific research, see L. Palazzani, *Innovation in scientific research and emerging technologies: a challenge to ethics and governance*, Cham (Switzerland), 2019, pp. 157.

[10] Risk/benefit proportionality is a general ethical requirement for clinical trials. See CIOMS, *Ethical Guidelines for Health-Related Research Involving Humans*, 2016, cit., Guideline 4, *Potential individual benefits and risks of research*: "For or research interventions or procedure that offer no potential individual benefits to participants, the risks must be minimized and appropriate in relation to the social and scientific value of knowledge to be gained (expected benefits to society from the generalizable knowledge)".

[11] See C. Petrini, *From bench to bedside and to health policies: ethics in translational research*, in Clinical Terapeutics, 162 (1), 2011, pp. 51-59, p. 52. See also C. Petrini, *Ethical Issues in Translational Research*, in *Perspectives in Biology and Medicine* 53 (4), 2010, pp. 517-533.

[12] There is a need to balance freedom of scientific research with respect for human dignity and human rights: "the risk in human research is that the emphasis on advancements in scientific knowledge might prevail over the protection of and the best interests of those who participate in research" (See C. Petrini, *From bench to bedside and to health policies: ethics in translational research*, cit., pp. 52-53).

risks/benefits), researchers have the responsibility to stop the study (even if research participants/patients request to continue). Furthermore, this can become particularly problematic when vulnerable population groups are enrolled in research (i.e. minors or fertile women). Even if the general ethical principle state that vulnerable individuals should be excluded from greater-than-minimal risk clinical trials[13], some documents stress the need to include them in research, so they can reap the benefits of their participation[14].

Acceleration in translating research results in medical practice does not mean disregarding the scientific soundness of findings and the reliability of the methods of analysis used to obtain such findings; therefore, all forms of research misconduct should be avoided, including conflicts of interests involving sponsors and those who administer experimental treatments (i.e. no pressure must be exerted by physicians and researchers, for professional reasons, on emotionally vulnerable individuals affected by severe, rare or life-threatening diseases[15]). Devising new ways to face the challenges of translational research through an adequate ethical oversight (providing for the participation of many experts, according to the type of research, in ethics committees) at the laboratory or preclinical research level is equally crucial, so as to be able to come up with rigorous safety criteria in making the decision to start first-in-human clinical trials and to guarantee that the acceleration of processes does not result in overlooking pivotal ethical issues. Alongside the undeniable opportunities linked to fostering the translation of laboratory findings into novel preventive, diagnostic and therapeutic options, translational research equally raises many ethical concerns with regard to guaranteeing an adequate protection of research participants, through appropriate safety assessments, in ways that avoid jeopardizing participants' health, especially in first in human clinical trials[16].

While translational research does not need to investigate completely novel routes to ethical reviews, it does perhaps call for the application of logic to identify the right procedures by applying the basic ethical values of research with human subjects to the specific context[17].

2. Translational research: international documents and guidelines

Within international recommendations and guidelines concerning biomedical and clinical research, some international documents address issues related to translational research. These documents

[13] See WORLD MEDICAL ASSOCIATION, *Declaration of Helsinki*, 1964 (last version 2013), cit., art. 20 ("Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research").

[14] In the latest version of CIOMS Guidelines, 2016, cit., we can read that "special protections are warranted to pregnant and breastfeeding women to ensure that their rights and interested are protected", when they are involved in scientific research (see J.J. VAN DELDEN, R. VAN DER GRAAF, *Revised CIOMS International Ethical Guidelines for Health-Related Research Involving Humans*, in *Journal of the American Medical Association*, 317(2), 2017, pp. 135-136.

[15] The case of therapeutic misconception – when the envisaged benefits of undergoing a clinical trial are overestimated and/or assimilated with a medical treatment – will be later discussed in this contribution (see par. 3).

[16] We will further deal with this issue in par. 5.

[17] C. PETRINI, *From bench to bedside and to health policies (and back): ethics in translational research*, in *Annali dell'Istituto Superiore di Sanità*, 50 (1), 2014, pp. 62-66, p. 66.

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underline mainly the three aspects: the importance of filling up the so-called "know-do gap"[18] between the laboratory/scientific side and the healthcare one; the blurred boundaries inside scientific research in itself, as the difference between basic research, clinical research and translational research has not clear boundaries; last but not least, the stress on safety for research participants, in particular in the case of the first testing of a drug on humans and when dealing with healthy volunteers, as it is in the case of experimental vaccines[19].

In the context of global health, the WHO in 2004 addressed translational research defining it in relation to the process of linking scientific knowledge to health care and in particular to public health. Translational research is there defined as "the process of applying ideas, insights, and discoveries generated through basic scientific inquiry to the treatment or prevention of human disease"[20]. According to the document, the culture and practice of health research should go beyond academic institutions and laboratories to involve health service providers, policymakers, the public and civil society; in order to respond more effectively at the national and global level to today's public health challenges, health research must be reoriented to strengthen health systems by translating knowledge into action to improve public health, besides attracting more investments for more innovative research on health systems. In this perspective, research is essential, but not sufficient, to decide which policies and practices to promote and implement. The notion of "knowledge for better health"[21] involves a continuous cycle of research, application and evaluation, and learning from that experience: stronger emphasis should be placed on translating knowledge into actions to improve health thereby bridging the gap between what is known and what is actually being done; as research should inform practice, practice should equally inform research. Improving health indeed requires the application of research, namely of biomedical sciences: in the "know-do gap" recalled by UNESCO International Bioethics Committee in 2010[22], there is the space of translational research, trying to join research and clinics and needing ethics guidelines for this scope and promoting the double-way road from research to clinical practice and backwards. *The European Research Infrastructure in Medicine* (EATRIS)[23] promotes translational research, trying to join the different worlds represented by ac-

[18] UNESCO INTERNATIONAL BIOETHICS COMMITTEE, *Report on Social Responsibility and Health* (2010), n. 50, available at https://unesdoc.unesco.org/ark:/48223/pf0000187899, last visited 08/04/2019.

[19] We will further deal with this aspect in par. 5.

[20] WHO, *World Report on Knowledge for Better Health* (2004), *Glossary of Terms*, p. 157, available at https://www.who.int/rpc/meetings/en/world_report_on_knowledge_for_better_health2.pdf, last visited 26/04/2019. Chapter 1 of the Report ("Learning to improve health") and chapter 4 ("Linking research to action") are particularly important for a general orientation about translational research.

[21] WHO, *World Report on Knowledge for Better Health*, cit., p. XV.

[22] From the perspective of Global Health Care, the International Bioethics Committee in 2010 highlighted that "there is a growing gap between medical knowledge and medical practice, sometimes referred to as 'know-do gap'. Millions of people have no access to proper health care. Even in developed countries, many well established preventive treatments are not used, resulting in complications and sometimes the need to use more expensive treatments when the preventable illness actually occurs. Many effective treatments are frequently underused or misused" (UNESCO INTERNATIONAL BIOETHICS COMMITTEE, *Report on Social Responsibility and Health*, 2010, cit., n. 50).

[23] Encouraged by the European Commission, in Europe EATRIS is one of the most important initiatives in order to promote translational research. Encouraged by the European Commission, EATRIS is a pan-European infrastructure whose main objective is to facilitate the translation of research findings into innovative products for

ademia and scientific researchers, industry and governments, in order to foster the transfer of scientific discoveries into feasible preventive and therapeutic strategies for disease at high socio-economic impact and relevant for national health plans[24]. EATRIS boosts the aim of accelerating innovation in life science and in the health care sector, by providing academia as well as industry easy and broad access to preclinical and clinical translational research infrastructure, to facilitate the development of new products and services in medicine along the entire research and development process up to the clinic[25]. It should be added that bridging the gap between scientific knowledge and development in the healthcare sector may imply different form of participation and the corresponding ethical requirements must be always fulfilled[26].

Concerning translational research insofar as it is defined in international and institutional documents, boundaries among the phases of research are blurred. The National Institute of Health (NIH)[27] consider together clinical and translational research, because the two areas overlap, with translational efforts often focusing on overcoming barriers that may impede the progress of clinical research. The NIH offers the following definition: "Translational research includes two areas of translation. One is the process of applying discoveries generated during research in the laboratory, and in preclinical studies, to the development of trials and studies in humans. The second area of translation concerns research aimed at enhancing the adoption of best practices in the community"[28]. Following this definition, NIH considers translational research as divided in two stages: the first is aapplying discoveries generated during research in the laboratory to the development of studies in humans. Such preclini-

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the prevention, diagnosis and treatment of diseases of particular public health significance and economic impact (www.eatris.eu, last visited April 26th, 2019; see also the presentation of EATRIS in ISTITUTO SUPERIORE DI SANITÀ, *Infrastructures for Translational Research on Health and the Role of Istituto Superiore di Sanità*, November 2014, cit., p. 6).

[24] "The coherent promotion of translational research for health represents a transnational primary objective for the scientific progress, for the economy and for the improvement of the quality/costs ratio of the national health service. In this context, the European Commission (EC) fostered the development of some Infrastructures for Biomedical Research, as instruments to speed up the transfer of scientific discoveries into innovation and measures for public health" (ISTITUTO SUPERIORE DI SANITÀ, *Infrastructures for Translational Research on Health and the Role of Istituto Superiore di Sanità*, cit., Preface).

[25] G. VAN DONGEN, A. USSI, F. DE MAN, G. MIGLIACCIO, E*ATRIS. A European initiative to boost translational biomedical research*, in *American Journal of Nuclear Medicine and Molecular Imaging*, 3 (2), 2013, pp. 166-174.

[26] The European Group on Ethics and New Technologies recommends that special attention should be given also to the new forms of engagement of the community and of citizen in science and in biomedical research, from an ethical point of view. Referring to the increasing direct involvement of citizens in science and medicine due to the emerging use of technologies in personal health, EGE recommends that "care should be taken when using terms such as citizen "engagement", "involvement" and "participation". First, because such labels may function as a form of branding for activities or endeavors where alternative interests (such as financial, for example) dominate; second, because an overriding focus on empowering potential of engagement (while certainly warranting investigation) can draw attention from the double-edged nature of citizen involvement, which carries risks of exploitation, manipulation and control", EUROPEAN GROUP ON ETHICS IN SCIENCE AND NEW TECHNOLOGIES (EGE), *The ethical implications of new health technologies and citizen participation. Opinion n. 29*, 2015, available at http://ec.europa.eu/research/ege/pdf/opinion-29_ege.pdf, last visited 26/04/2019, p. 25.

[27] NATIONAL INSTITUTE OF HEALTH, *Biennial Report of the Director*, 2006-2007, cit.

[28] NATIONAL INSTITUTE OF HEALTH, *Definitions under Subsection 1-Research Objectives*, Institutional Clinical and Translational Science Award, 2007, available at https://grants.nih.gov/grants/guide/rfa-files/RFA-RM-07-007.html, last visited 08/04/2019.

cal translational investigations are often carried out using animal models, cell cultures, samples of human or animal cells, or experimental systems; the second, taking results from studies in humans and applying them to research on enhancing the adoption of best practices in the community. Furthermore, in the Translational Science Spectrum[29], NIH includes each stage of research along the path from the biological basis of health and disease to interventions that improve the health of individuals and the public. In NIH's perspective, the distinction is between different phases, i.e. basic research, pre-clinical research, clinical research, clinical implementation and public health. Basic research scientists provide clinicians with new tools that can be used for patients, and clinical researchers make new observations about the nature and progression of disease that often stimulate basic investigations. Research on new outreach approaches and the *cost-effectiveness* and *real world* feasibility of prevention and treatment strategies are important aspects of this endeavor, as they provide the feedback necessary to ensure the practicality of interventions. Translational research goes beyond clinical research, implementing the relation between research and health, including public health, as mentioned above. Also *The European Science Foundation* (ESF) explicitly deals with translational research and particularly with the difficulty to set clear boundaries between basic research and clinical research[30]. In addition, the EGE Statement on gene editing[31], in addressing the ethically problematic issues surrounding gene editing, points out how challenging it can be to provide a clear distinction between basic and translational research. In the context of germline gene modification, the EGE notably stresses that: "It has been suggested that research with a clinical application, as distinct from basic research, should be subject to a moratorium. We would be cautious in terms of whether such a clear-cut distinction can be made between basic and translational research. Likewise, the blurring of the lines between clinical applications in pursuit of therapeutic or enhancement goals (albeit the ethical issues pertaining to each may be different), must be considered"[32]. Moreover, in another part of the statement, the European Group on Ethics underlines once again that "because of the blurring lines between basic and applied research, some also call for a moratorium on any basic research involving human germline gene modification until the regulatory framework is adjusted to the new possibilities"[33].

Concerning safety of research participants, CIOMS guidelines heighten the importance of translational research, implementing relations between basic research advances and their use, in order to develop new therapies or medical procedures[34], as already recalled above. Particularly significant for translational research are the elements regarding *Potential individual benefits and risks of research* (Guideline 4), which is a central aspect for translational research because translational research has the aim to gain new scientific knowledge, ensuring at the same time research participants' safety. The Guideline recommends that potential individual benefits and risks of research must be evaluated

[29] National Institute of Health, *Translational Science Spectrum*, 2015, cit.

[30] The European Science Foundation (ESF), *Implementation of Medical Research in Clinical Practice*, 2011, cit.

[31] European Group on Ethics in Science and New Technologies (EGE), *Statement on Gene Editing*, 2016, available at https://ec.europa.eu/research/ege/pdf/gene_editing_ege_statement.pdf, last visited 08/04/2019, pp. 2.

[32] European Group on Ethics in Science and New Technologies (EGE), *Statement on Gene Editing*, cit., p. 1.

[33] European Group on Ethics in Science and New Technologies (EGE), *Statement on Gene Editing*, cit., p. 2.

[34] See CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, cit., *Preface*. All the guidelines are relevant for translational research.

in a two-step process[35]: as first step, the potential individual benefits and risks of research must be evaluated; as a second one, the aggregate risks and potential individual benefits of the entire study must be assessed[36]. The aggregate risks of all research interventions or procedures in a study must be considered appropriate in light of the potential individual benefits to participants and the scientific social value of the research. In addition, also Guideline 5 (*Choice of control in clinical trials*) is particularly important in the context of translational research. As a matter of fact, translational research involves patients in testing new therapies or drugs and for this reason a control group is needed; this is why this Guideline is relevant for translational research. As a general rule, the research ethics committee must ensure that research participants in the control group of a trial of diagnostic, therapeutic, or preventive intervention receive an established effective intervention. Placebo may be used as a comparator when there are compelling scientific reasons for using it (this is when a trial cannot distinguish an effective intervention from an ineffective one without using placebo) and when delaying or withholding the established effective intervention will result in no more than a minor increase above minimal risk to the participant and risks are minimised[37]. CIOMS Guideline 6 (*Caring for participants' health needs*) regards translational research as it underlines that care for research participants must be adequately addressed by researchers and sponsors. Researchers and sponsors must show care and concern for the health and welfare of study participants because research with humans often involves interactions that enable researchers to detect or diagnose health problems during recruitment and the conduct of research; furthermore, clinical research often involves care and preventive measures in addition to the experimental interventions. In some cases, participants may continue to need the care or prevention provided during the research after their participation in the study has ended. This may include access to an investigational intervention that has demonstrated significant benefit. The Guideline recommends to include in the informed consent process the information on care for participants' health needs, during and after the research[38].

3. Informed consent in translational research

In the context of translational research, informed consent plays a central and specific role. As in biomedical research in general, "informed consent should be understood as a process, and participants

[35] See CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, cit., Guideline 4 (*Potential individual benefits and risks of research*).

[36] For research that includes potential individual benefits for the participants, risks are acceptable if they are minimized and outweighed in consideration of the potential benefits for the participants; for research interventions or procedures that offer no potential individual benefits to participants, the risks must be minimized and appropriate in relation to the social and scientific value of the knowledge to be gained (expected benefits to society from the generalizable knowledge (see CIOMS, cit., Guideline 4, *Potential individual benefits and risks of research*).

[37] See CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, cit., Guideline 5, *Choice of control in clinical trials*).

[38] See CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, cit., Guideline 6, *Caring for participants' health needs*).

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have a right to withdraw at any point in the study without retribution"[39]. Starting from the ethical issues related to translational research, namely uncertainty, risk, safety of research participants, three specific points should be underlined, in particular: risk communication, which is of paramount importance in the case of translational research; the patient-physician relationship; informed consent obtained from healthy volunteers, as it is the case of experimental vaccines. We will also offer a brief reference to informed consent during disease outbreaks, a situation which may require the use of unproven treatments.

Subjects involved in a translational/clinical trial have to understand the exploratory nature of the study: namely, the fact that it does not have a direct therapeutic objective and that it entails risks, potential and possible direct or indirect benefits. If volunteers misunderstand this, they provide invalid informed consent. As in general, in non-therapeutic studies individuals must give voluntary and written consent[40]. Scientific research may either have a potential direct benefit for the patient (for instance, the case of experimental treatments) or a potential indirect benefit deriving from the goal to obtain a general finding for medical research and subsequently for society or certain groups of persons. In situations with no direct benefit, the assessment and consideration of risk is of special importance, notably when research undergoes an accelerated process, as in the context of translational research: all forms of research, which are not directly beneficial to the person concerned are usually only permissible if they bear no risk/burden or only minimal risk/burden. This is far more true in the case of enrolling particularly vulnerable human participants, who require special protection by researchers, due to their specific health condition (i.e. pregnant women) or because they are unable to consent (i.e. minors). However, precautions towards vulnerable populations, which are necessary in many respects, might also significantly restrict the range of research options for the benefit of the groups of persons concerned and consequently deprive them of adequate opportunities stemming from medical progress.

Effective strategies of risk communication (in terms of accuracy, clarity and understandability, tailored to different health literacy levels, age/gender and cultural backgrounds) are key to ensuring human subjects' full and critical awareness of the extent of risk involved in a specific type of research (i.e. with regard to its nature and specific phase) and providing them with the necessary information to make a conscious decision in participating to the study with respect to the possible consequences of their enrolment, while overcoming misconception barriers linked to gaps at any stage of the informed consent process. Respecting the autonomy of participants in translational research requires an even more careful and effective handling of the informed consent process, by envisaging a differentiated approach to information, adapted to the benefits and risks related to the specific research

[39] CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, cit., Guideline 9, *Individuals capable of giving informed consent*. As know the principle of informed consent in biomedical research has its origins on in the international institutional level in the Declaration of Helsinki, 1964, last revision 2013.

[40] WHO, *Guidelines for good clinical practices (GCP) for trials on pharmaceutical products* (1995), available at https://apps.who.int/medicinedocs/pdf/whozip13e/whozip13e.pdf, last visited April 26th, 2019. The document contains useful reference to informed consent in clinical trials: in a non-therapeutic study, i.e. when there is no direct clinical benefit to the subject, consent must always be given by the subject and documented by his or her signature.

study and research phase provided before, during and after the study. If not addressed, communication barriers between the participants and the researchers may influence comprehension of potential benefits and risks related to clinical studies, leading to misconceptions with respect to an overestimation of envisaged benefits deriving from inclusion in a clinical trial (the so-called "therapeutic misconception"[41]) or in general for the expectation of receiving health services in the context of severely resource constraints public health systems[42].

Another specific aspect of translational research concerns the fact that it presupposes the connection between research and medical practice, highlighting the importance, from an ethical point of view, of strengthening the doctor-patient relationship, in order to facilitate the patient's understanding of the differences between what is therapy and what is research and the existence of possible "nuanced boundaries" between the two. In this perspective, informed consent is a double way process: "Informed consent is a two-way communicative process that begins when initial contact is made with a potential participant and ends when consent is provided and documented, but can be revisited later during the conduct of the study. Each individual must be given as much time as needed to reach a decision, including time for consultation with family members or others. Adequate time and resources must be provided for informed-consent procedures"[43]. Fostering communication strategies to improve the physician-patient relationship is essential in this context (notably in moving backwards from "bedside to the bench"), in order to ensure the "circularity of information" (not only from the physician to the patient, but also from the patient to the physician) and increase health benefits for the community as a whole: for instance, improving patient communication of possible adverse events related to experimental or validated drugs, also after the end of a research study or a medical treatment. Communication of risks is very important as CIOMS recommends in general[44]. Whenever new evidence arises, in any phase of research, with regard to specific risks for research participants, they should be immediately informed and reminded of their right to revoke consent without any negative consequences in terms of cure and care for them. Researchers have the duty to fully inform research participants about the nature and extent of increased risk for their health, in case they decide to stay/remain in the research. Researcher should assure freedom for research participants to withdraw from it at any time, without any negative consequences.

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[41] See C. PETRINI, *From bench to bedside and to health policies (and back): ethics in translational research*, cit., p. 66, par. on "Therapeutic misconception").

[42] Among i-CONSENT findings, D1.7, *Socio-cultural, psychological and behavioral perspectives toward informed consent process*, available at https://i-consentproject.eu/wp-content/uploads/2019/01/D1.7-Sociocultural-psychological-and-behavioural-perspectives-towards-informed-consent-process.pdf, last visited 26/04/2019, explicitly deals with this aspect from a socio-cultural point of view, in particular in section n. 4.4, "Therapeutic misconceptions and unrealistic optimism in clinical trials", pp. 49-54.

[43] CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, cit., *Commentary on Guideline 9, Individuals capable of giving informed consent*.

[44] "Researchers must be completely objective in discussing the details of the experimental intervention, the pain or discomfort it may entail, and known risks and possible hazards. In some types of prevention research, potential participants must receive counselling about risks of acquiring a disease and steps they can take to reduce those risks. This is especially true of preventive research on communicable diseases, such as HIV/AIDS" (CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, cit., Commentary on Guideline 9, *Individuals capable of giving informed consent*).

General orientations for the obtaining of informed consent are valid for patients and for healthy volunteers[45] as well. Clinical trials for experimental vaccines can be considered part of translational research, as an example of clinical research involving humans; in this specific case, researchers deal with healthy volunteers. Vaccine trials fall within interventional research and they are not "low interventional studies" with minimal risk. The fact that such trials involve healthy subjects determines two consequences: a stringent emphasis on safety both in clinical trials and in clinical practice, and a more rigid regulation concerning informed consent. A rigorous regulatory procedure ensures quality, efficacy and safety; within the European Union human vaccines are regulated by European Medicines Agency (EMA). In the case of healthy subjects taking part in a translational/clinical research, informed consent must enable the subject to understand that early stages of clinical trials do not primarily have a therapeutic objective, since the core focus remains on safety[46]. Accordingly, risk communication must be deepened and carefully assessed. In the case of healthy volunteers involved in research on non-therapeutic treatments (such as experimental vaccines), the informed consent should explicitly refer to the absence of undue inducement or compensation, which may lead them to underestimate the risks linked to participation.

Translational research, accelerating the process from the lab side to treatment, includes also the reference to the use of unproven interventions, such as the case of the using of vaccine in disease outbreaks. WHO held and reported discussions regarding ethical issues in the evaluation of Ebola vaccines, regarding informed consent and whom priority recipients might be. The document stresses that "in the particular context of the current Ebola outbreak in West Africa, it is ethically acceptable to offer unproven interventions that have shown promising results in the laboratory and in animal models but have not yet been evaluated for safety and efficacy in humans as potential treatment or prevention"[47]. In this report for the WHO, ethical, scientific and pragmatic criteria are underlined and it is recommended transparency about all aspects of care, so that the maximum information is ob-

[45] On the inclusion of healthy volunteers in clinical trials, the International Bioethics Committee in 2008 recalled that "in dealing with healthy volunteers, the significant fact is that those persons have not, in the first place, requested care/involvement in a medical procedure. They agree to be part of research, either for altruistic reasons or to seek compensation in some other way. The risks involved in the research should be minimized. A description of the research procedures, known risks, uncertainties and participant responsibilities should be provided in order to achieve informed consent. Undue incentives should not be offered to participants and adequate insurance covering adverse events and outcomes should be provided. Participation should be described in precise terms in writing and written informed consent should be mandatory" (UNESCO INTERNATIONAL BIOETHICS COMMITTEE, *Report On Consent*, 2008, available at https://unesdoc.unesco.org/ark:/48223/pf0000178124, last visited April 26th, 2019, n. 42).

[46] A specific reference on the topic of safety of medicinal products is EUROPEAN MEDICINES AGENCY, *Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Clinical Trials with Investigational Medicinal Products*, 2007 and its first revision (July 2017), available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf, last visited April 26th, 2019. In the document, strategies for mitigating and managing risks are envisaged, including principles on the calculation of the starting dose to be used in humans, the subsequent dose escalations, the criteria for maximum dose and the conduct of the trial inclusive of multiple parts.

[47] WHO, Ethical considerations for use of unregistered interventions for Ebola viral disease: report of an advisory panel to WHO, 2014, available at https://www.who.int/csr/resources/publications/ebola/ethical-considerations/en/, last visited April 26th, 2019.

tained about the effects of the interventions, fairness, promotion of cosmopolitan solidarity, informed consent, freedom of choice, confidentiality, respect for the person, preservation of dignity, involvement of the community and risk–benefit assessment. If and when unproven interventions that have not yet been evaluated for safety and efficacy in humans but have shown promising results in the laboratory and in animal models are used to treat patients, those involved have a moral obligation to collect and share all the scientifically relevant data generated, including from treatments provided for "compassionate use". On the same topic, EGE recalls the 2014 outbreak of Ebola in Africa as an example of expanded access to treatment: in response to this challenge WHO convened a consultation to consider and address the ethical implications of use of unregistered treatments. Aside from scientific criteria, certain ethical criteria must guide the use of such treatment: transparency, informed consent, freedom of choice, confidentiality, respect for individuals, preservation of dignity, fair distribution and involvement of the community. In addition, all scientifically relevant data from this intervention should be collected and shared to establish the safety and efficacy of the intervention[48].

4. Analogies and differences between innovative therapies and translational research

There is an increasing shift from the 'evidence-based' medicine model (e.g. which focuses on using randomized clinical trials to establish the best treatment for the average patient) to the "personalized medicine" model or "stratified/precision medicine" model (e.g., which considers differences among individual patients or homogeneous groups), even though they are both currently implemented in clinical practice.

Innovative therapies can be placed in the context of blurred boundaries between research and treatment, which is a common element that these therapies share with translational research. Innovative therapies coincide with different categories, one of which may fall under translational research, which is the case of o*ff-label treatment.* It refers to "the use of treatments which differ from those authorised, with a scientific basis of efficacy and tolerability"[49]. In this sense, it is not far from traditional standards of experimentation and use of drugs, "but allows, exceptionally, under medical control, the use of treatments not yet validated by healthcare regulatory authorities in cases where patients have a serious pathology without validated therapies or with validated therapies which are not effective"[50]. In addition, promoting translational research of advanced therapies has become a priority for scientific communities and national governments[51].

[48] European Group on Ethics in Science and New Technologies (Ege), *The ethical implications of new health technologies and citizen participation. Opinion n. 29*, 2015, cit., p. 27.

[49] European Group on Ethics in Science and New Technologies (Ege), *The ethical implications of new health technologies and citizen participation*, 2015, cit.

[50] European Group on Ethics in Science and New Technologies (Ege), *The ethical implications of new health technologies and citizen participation*, 2015, cit.

[51] F. Belardelli, P. Rizza, F. Moretti, C. Carella, M.C. Galli, G. Migliaccio, *Translational research on advanced therapies*, in *Annali dell'Istituto Superiore di Sanità*, 47 (1), 2011, pp. 72-78. Advanced therapy medicinal products (ATMP) are a new medicinal product category comprising gene therapy and cell-based medicinal products as well as tissue engineered medicinal products.

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Despite this commonality, a number of differences can equally be devised between innovative therapies and translational research, when considering the category of the so-called 'compassionate use' of drugs: in this case, an innovative therapy is "a newly introduced or modified therapy with unproven effects. Unlike research, which follows a predetermined course of action set out in a protocol, experimental or innovative therapy involves a more speculative approach to the patient's care and may be adapted to the individual's response"[52]. Non-validated treatments are usually used as a well-motivated and strictly monitored exception, in front of a life-threatening situation or a particularly severe disease and when there are no recognised effective alternatives in terms of treatments, always with an approval by the Ethics Committee; in addition, non-validated treatments are for personal and non-repetitive use (e.g., it involves the use of individual or group treatments). Such compassionate use drugs must have a reasonable scientific basis (i.e. data published in international scientific journals, results on animals and preferably results from phase I clinical trials). The prescription requires an adequate assessment by a panel of experts, under full transparency conditions, without conflicts of interest, ensuring publication of the products' composition and the treatment's results, along with a detailed explanation to the patients of the potential dangers, and possible lack of benefits, as well as the drugs' risks and costs[53].

Translational research does not concern exceptional situations involving a single research participant or patient, without validated treatments as an alternative, but clinical trials with cohorts of volunteers, in order to seek and test better therapeutic opportunities.

5. The primary duty of safety for research participants in the leap from bench to bedside

First-in man (or "first-in-human") trials are trials with no specific therapeutic objective. They are one of the principal means of translational research and are regulated by soft law orientations. The first-in-human clinical trial is a critical turning point between preclinical studies and first human exposure

[52] The Nuffield Council on Bioethics, *Topic summary: innovative therapies*, 2016.

[53] Innovative therapies may raise a set of ethical problems deriving from the blurred distinction between research and treatment: researchers and physicians involved in innovative therapies should focus on fostering the doctor-patient relationship and avoiding putting it at risk because of possible conflicts between ensuring developments in the medical field and protecting the welfare of patients, since patients may perceive their role as being instrumentalised for experimental or professional goals; it may also occur that patients welcome enthusiastically the possibility to start experimental treatments, while overlooking the risks, as they consider these therapies as a "last resort" option/hope to get better; the patient's ability to express an actual informed consent may be undermined by his/her emotional condition related to being affected by an incurable and life-threatening disease; understanding whether there is a duty for health professionals involved in innovative therapies to share the information regarding positive and negative results of interventions (e.g. this data may be useful for other patients, who could be informed about evidence-based benefits and risks, or to improve future research programs) may become problematic, as well as envisaging ways to implement this duty; equal access to innovative therapies might be another problem (e.g. only those patients that voluntarily seek or have access to sources of information on these experimental treatments are likely to rely on these therapies); health professionals may be put under pressure, because patients constantly request these experimental treatments, after having collected information on their own.

and subsequent larger clinical trials in hundreds or (for many vaccines) thousands of subjects[54]. For sponsors, relevant risk assessment for first-in-human clinical studies means careful design and conduct of studies that reduce potential risk to humans. In the case of vaccines, the target population for vaccine trials is healthy volunteers and this requires special carefulness concerning benefit/risk assessment. A balanced approach for first-in-human studies of a novel vaccine candidate is crucial to ensure safety of the participants in the trial. Hence, safety for research participants is the most relevant issue at stake when a novel drug or vaccine is for the first time tested on human beings.

The protection of clinical trial subjects is consistent with the principles set out in the Declaration of Helsinki[55]. Concerning issues related to the general duty to protect the subjects who take part in medical research[56] and to implement measures to minimize risk[57], the Declaration states that while the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects (see article 8); in particular, physicians who combine medical research with medical care should involve their patients in research, only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects (see article 14). In addition, the ICH Guidelines contain references to research involving humans[58]. In particular, as already recalled, Guideline E6 ("Good Clinical Practice") describes the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and Ethics Committee/Independent Review Boards[59]. Safety for research participants is recommended as a primary duty also from the WHO: by providing a basis both for the scientific and ethical integrity of research involving human subjects, the WHO *Guidelines for good clinical practice (GCP) for trials on pharmaceutical products*[60] recommend the protection of the rights and safety of subjects, including patients, and that the investigations be directed to the advancement of public health objectives[61].

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[54] K.B. GOETZ, M. PFLEIDERER, C.K. SCHNEIDER, *First-in-human clinical trial with vaccines – what regulators want*, in *Nature Biotechnology*, 28 (9), 2010, pp. 910-916: "For sponsors, relevant risk assessment for first-in-human clinical studies means careful design and conduct of studies that reduce potential risk to humans. In comparison to therapeutic proteins or other medicinal products, however, the prophylactic character and mechanism of action of vaccines warrant particular attention" (p. 910).

[55] WORLD MEDICAL ASSOCIATION, *Declaration of Helsinki* (1964, current version 2013), cit.

[56] See WORLD MEDICAL ASSOCIATION, *Declaration of Helsinki*, cit., in particular articles 4, 6 and 7.

[57] See WORLD MEDICAL ASSOCIATION, *Declaration of Helsinki*, cit., in particular articles 16-18.

[58] In particular, among the INTERNATIONAL CONFERENCE ON HARMONISATION (ICH) *Efficacy Guidelines*, which concern the design, conduct, safety and reporting of clinical trials, we remind here: Pharmacovigilance (E2A-E2F) (1994); Good Clinical Practice (E6) (1996, amended in 2016); General Considerations on Clinical Trials (E8) (1997); Choice of Control Group in Clinical Trials (E10) (2000); Clinical Trials in Paediatric Population (E11-E11A) (2000).

[59] In ICH guidance, there are references to informed consent, intended as a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate; IC can be oral or written, and it must be documented (ICH, *Guideline on Good Clinical Practice* (E6), 1996, n. 1.28).

[60] WHO, *Guidelines for good clinical practice (GCP) for trials on pharmaceutical products*, 1995, cit.

[61] The Guidelines also recall that the investigator must take appropriate measures to ensure the safety of clinical trial subjects, underlying in particular that in research on man, the interest of science and society should

A specific reference on this topic of FIM is the EMA *Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Clinical Trials with Investigational Medicinal Products*[62]. The revision is intended to further assist stakeholders in the transition from non-clinical to early clinical development and in identifying factors influencing risk for new investigational medicinal products. This Guideline has the aim to increase the regulations on safety of the first testing of a drugs or a vaccine. In the document, strategies for mitigating and managing risks are envisaged, including principles on the calculation of the starting dose to be used in humans, the subsequent dose escalations, the criteria for maximum dose and the conduct of the trial inclusive of multiple parts: first in man studies have mainly the scope of establishing this criteria, in order to be then followed from by the subsequent phases of the clinical trial. The EMA Guideline recommends that the safety and well-being of trial subjects (be they patients or healthy volunteers) should always be the priority and special consideration should be given to characterising risk and putting in place appropriate strategies to minimise risk; it also aims to address as far as possible the important issues that may need consideration during the process of designing a set of studies in a clinical development programme, such as quality aspects, nonclinical aspects, dosing selection.

The early clinical development of human medicinal products has an intrinsic element of uncertainty in relation to both the possible benefits and risks of a novel drug candidate. Uncertainty may arise from particular knowledge, or lack thereof, regarding the mode of action of the Investigational Medical Product, the presence or absence of biomarkers, the nature of the target, the relevance of available animal models and/or findings in non-clinical safety studies. In addition, risks may derive from the characteristics of the population to be studied, whether healthy volunteers or patients, including potential genetic and phenotypic polymorphisms influencing Pharmacodynamics and Pharmacokinetics. For these reasons, careful dosing selection of an Investigational Medical Product is a vital element to safeguard the subjects participating in First-In-Human and early Clinical Trials. Special attention should be given to the estimation of the exposure to be reached, at the initial dose to be used in humans, and to subsequent dose escalations to a predefined maximum expected exposure. The expected exposure in humans at a dose to be given, in comparison to the exposure at which certain effects were observed in animals or earlier in the study in humans, is considered more relevant than the relative dose levels between animals and humans[63]. EMA recommends that trials should be designed in a way that optimises the knowledge to be gained from the study without exposing excessive numbers of subjects while ensuring the safety of participants; the overall study design should justify the inclusion of each study part considering the data each will provide and the time available for integrated assessment. Safety should not be compromised in the interests of speed of acquiring data or for logistical reasons and risk mitigation activities should be proportionate to the degree of

never take precedence over considerations related to the wellbeing of the subject (WHO, *Guidelines for good clinical practice (GCP) for trials on pharmaceutical products*, 1995, cit., Annex 1).

[62] EUROPEAN MEDICINES AGENCY (EMA), *Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Clinical Trials with Investigational Medicinal Products*, 2007 (first revision July 2017), cit.

[63] The contents of EUROPEAN MEDICINES AGENCY (EMA), *Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Clinical Trials with Investigational Medicinal Products*, 2007 (first revision July 2017) are recalled and discussed in K.B. GOETZ, M. PFLEIDERER, C.K. SCHNEIDER, *First-in-human clinical trial with vaccines – what regulators want*, 2016, cit., pp. 910-916.

uncertainty and the potential risks identified. Following the EMA Guideline, it should be added that the choice of subjects (healthy volunteers as well as patients), among other ranges, includes a patient's ability to benefit from other products or interventions, the predicted therapeutic window of the Investigational Medical Product, and factors relating to special populations, including age, gender, ethnicity and genotype(s). A balanced and reasonable approach for first-in-human studies of a novel drug or vaccine candidate is crucial to ensure safety of trial participants. The principles of the EMA guideline need to be applied in a reasonable and scientific way based on how prophylactic and therapeutic vaccines against infectious diseases function[64].

The Council of Europe[65], although it does not refers explicitly to translational research or first-in-human trials, offers references regarding ethical issues related to research involving humans: research involving humans must justify the proposal to conduct the research in human beings and this not only as far as the research has the aim of improving people's health but also showing that similar results cannot reasonably be obtained by other means, for example by mathematical modelling or research in animals; researchers who plan to recruit healthy volunteers must abide by the general ethical principles pertaining to biomedical research; the Research Ethics Committee must be satisfied that the research will entail no more than acceptable risk and acceptable burden for those participants. For safety reasons, it is advisable to restrict the number of participations for each individual volunteer; for any biomedical research involving human beings, the researchers must ensure that the risks and burdens of research participation are not disproportionate to any potential benefits. Risks and burden should always be minimised; biomedical research involving interventions must not be allowed to proceed unless the potential research participant has given his or her consent.

[64] K.B. Goetz, M. Pfleiderer, C.K. Schneider, *First-in-human clinical trial with vaccines – what regulators want, in Nature Biotechnology*, 2016, cit., p. 916.

[65] The Council of Europe-Steering Committee on Bioethics, *Guide for Research Ethics Committee Members* (2010), par. 6.C.2, p. 29.

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Legal Aspects of Informed Consent in Clinical Research: the Case of Vaccinations in the International Legal Framework

Valeria Ferro*

ABSTRACT: Informed consent is an essential prerequisite in clinical trials. The goal of the informed consent process is to provide appropriate information, so that the potential participant can make an informed decision about whether or not to enrol in a trial. Information must concern the explanation of the research status, its objectives, a description of benefits and risks, alternative treatment that may be available, and the subject's rights and responsibilities. After a review of the main regulatory instruments on informed consent, the article analyses the EU regulatory framework for vaccines. In a second part, the issue of voluntariness and validity of informed consent in case of compulsory vaccination is discussed, through an examination of selected national rules (France, Spain, Italy, and Germany).

KEYWORDS: Informed consent; clinical trials; law; vaccines; public health and human rights

SUMMARY: 1. Informed consent in phase 1-4 clinical trials – 2. Informed consent in clinical research: hard law measures – 3. Vaccine trials in European legal framework – 3.1. Mandatory vaccination and ethical issues: the case of compulsory vaccination in France, Germany, Italy, Spain.

1. Informed consent in phase 1-4 clinical trials

Communication of risks and benefits is a fundamental aspect of the informed consent process in clinical trials in order to guarantee an informed decision making by the potential participant. The assessment of the risks and benefits comprehension is for this reason a critical component of regulatory requirements for clinical trials conduct. The Clinical Trial Regulation[1] introduced different risk categories for clinical trials.

Since 1940s, the scientific community has drawn up a distinction in phases of clinical research, which is accepted by European laws. The initial stage is defined "preclinical" research, not done with people, but it involves laboratory studies (in vitro) and tests on animals. This step of the study includes an investigation of the possible toxic and/or teratogenic effects. Functions of the physiological sys-

* *Ph.D. Libera Università Maria Ss. Assunta (LUMSA), Palermo. E-mail*: v.ferro@lumsa.it. *The article was subject to a double-blind peer review process.*

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[1] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials in medicinal products for human use and repealing Directive 2001/20/EC.

tems are investigated, and the investigator must provide a general pharmacological characterization of the drug, with particular reference to adverse reactions (Pharmacodynamics). After preclinical studies that provide evidence of safety, the substance is at first tested in trials involving healthy human volunteers. In phase 1-4 clinical trials the efficacy of an investigational product is explored in a patient population which has been selected according to inclusion and exclusion criteria.

Depending on the phase and the object of the clinical trials, the level of risk and its communication change. Anyhow, informed consent must be obtained before procedures and treatments are performed.

In Phase I, the patients involved have significant possibilities to experiment serious side effects[2]. They must be adequately informed before they consent to participate. The duty of investigators to inform in this stage is very strict. Phase I studies assess the safety and tolerance of a drug. This initial phase of testing includes a small number of healthy volunteers (20 to 100). The study is designed to determine the effects of the drug on humans including how it is absorbed by the subject. In this step side effects are analysed. The process of patient recruitment and informed consent is governed by laws to ensure the rights, safety, and well-being of participants. Previously the Directive 2001/20/EC[3] and then the Regulation (EC) No. 536/2014 established that it is necessary to make provision for the monitoring of adverse reactions occurring during the clinical trials using Community surveillance procedures, in order to ensure the immediate cessation of any clinical trial in which there is an unacceptable level of risk. Legal requirements are honesty regarding the nature of participation in clinical research and honesty regarding the level of the risk. Science and experimentation must demonstrate formal, ethical and methodological correctness. Patients involved in the clinical trial must represent the future category of subjects to whom the drug can be administered, but women and children are usually excluded from this phase of experimentation. The Regulation (EU) No 536/2014 on clinical trials of medicinal products for human use introduced requirements for taking account of gender in trials, but the procedure is to involve only men in the first phase of clinical trials, with particular attention to life expectancy, performance status and organ function. Concerning the inclusion criteria to participate in a clinical trial, the European Parliament, with the resolution of 14 February 2017 on promoting gender equality in mental health and clinical research (2016/2096(INI)), calls on the Member States, when applying Regulation (EU) No 536/2014, to use a methodological approach for clinical trials. This approach would guarantee an adequate representation of men and women.

Phase II is needed to confirm drug has therapeutic effect, to determine optimal dose, to determine correct frequency dosing. This second phase involves up to several hundred patients. Most phase II studies are randomized trials where one group of patients receives the experimental drug, while a second "control" group receives a standard treatment or placebo. Often these studies are "blinded": neither the patients nor the researchers know who has received the experimental drug.

[2] B. Goetz Karen, M. Pfleiderer & c. K. Schneider, *First-in-human clinical trial with vaccines – what regulators want*, in *Nature Biotechnology*, 2010, pp. 910-916.

[3] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the application of good clinical practice in the conduct of clinical trials with medicinal products for human use.

Phase III compares the effects of a new treatment with standard treatment, finding out efficacy of the drug and effects or risks and safety in the long term. It is required a large number of volunteers/ patients (several hundred or thousand) to provide significant clinical and statistical power. Concerning phase II and phase III of clinic trials, gender and age-related aspects are not addressed and there are no specific legal provisions about obtaining informed consent in these steps.

Phase IV of clinical trials studies the drug after it has received a Product Licence – drug marketed. From Clinical Trials Regulation's perspective, the studies of this stage are "non-interventional" that investigate various aspects of drug use including efficacy and safety under real life conditions. Pharmacovigilance is the field of public health research that studies the effects of medicinal products in large populations. The specific objective of this stage is to evaluate drug's long-term effectiveness and impact on a patient's quality of life. In this sense, pharmacovigilance is non-interventional research. The informed consent is also necessary for non-interventional studies. The content of informed consent in phase IV of clinical trials is different compared to that of earlier phases, but participant's participation remains informed and voluntary.

The European legal framework of pharmacovigilance for medicines for human use marketed within the EU is provided for in Regulation (EU) No. 726/2004[4], as amended by Regulation (EU) No. 1235/2010[5], and in the Directive 2001/83/EC[6], as amended by Directive 2001/84/EC. Title IV of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use contains the provisions applied for the authorisation for the manufacture of medicinal products as part of the requirements needed for the application for a marketing authorisation. The marketing authorization rules guarantee the quality assessment. The competent authority of the Member State issues manufacturing authorization. Pharmacovigilance in also governed by Commission Implementing Regulation (EU) No. 520/2012[7].

This body of legislation aims to strengthen public health through improved prevention, detection and assessment of adverse reactions. New legislation for pharmacovigilance is supported by a new guidance on good pharmacovigilance practices (GVP), a new set of guidelines for the conduct of pharmacovigilance in the EU. The pharmacovigilance legal requirements and GVP apply to all medicinal products authorised in the EU, whether centrally or nationally authorised. While risk proportionality underpins the new legislation, the requirements are generally the same for different types of product. Pharmacovigilance is an essential part of pharmaceutical product development and commercialization. All safety aspects must be monitored properly through a systematic approach. Benefit and risk must be continually assessed as more is learned about the product through its use. Informed consent, in phase IV, essentially comprises a data privacy clause, there are no additional diagnostic

[4] Regulation (EU) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

[5] Regulation (EU) No. 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use.

[6] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

[7] Regulation (EU) No. 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council.

tests or invasive procedures. The patients should report adverse drug reactions directly to the national competent authorities.
These legal requirements concerning clinical trials established by the aforementioned European laws apply for clinical trials in general and thus also for vaccine trials, although they are not specific for vaccines.

2. Informed consent in clinical research: hard law measures

The principle of informed consent is declared, at international level, in the Convention on Human Rights and Biomedicine (Oviedo, 1997)[8], that represents a milestone in the protection of human rights in biomedical field. The content of the Oviedo Convention is supplemented by various Additional Protocols, such as Additional Protocol concerning biomedical research (2005)[9], with a view to protecting human rights and dignity in the specific field of biomedical research. Chapter II (articles 5 to 9) addresses the need for informed consent before any biomedical intervention. Refusal to give consent or the withdrawal of consent to participation in research must not lead to any form of discrimination against the person concerned, in particular regarding the right to medical care. The Convention provides particular protection of people who are not able to consent, due to either their age (minors) or their mental incapacity (article 6), and of people who have a mental disorder (article 7). Research on pregnant or breastfeeding women is covered by the Protocol (Chapter VI). Article 18 describes the conditions in which research on pregnant women may be undertaken.
At European level, the analysis of hard law measures starts from the Directive 2001/20/EC of 4 April 2001 ("the Clinical Trial Directive"), that legally ensured the implementation of the principles of good clinical practice in clinical trials on medicinal products in Europe. Several articles in the Directive provided guidance regarding the protection of clinical trial subjects. With specific regard to informed consent, article 3 of the Directive provided for legal guarantees. Participants must give a written consent (or oral if he/she is unable to write) after being informed of the significance, nature, implications and risks of the clinical trial. The National transpositions by the Member States, in compliance with the directive, showed the importance of understanding the informed consent process as a whole, and the right of participants to have sufficient information about the research and any risks they may encounter. A common element in any transposition law regarding clinical trials on human beings was the requirement of proportionality. This principle, along with that of prevalence of the subject's welfare over the interests of science and community, could be found in the Council of Europe's Convention on Human Rights and Biomedicine and in the 2001/20/EC Directive. However, the transposition of the Directive across EU countries has led to uneven application. For this reason the Clinical Trial Directive has been replaced by the Clinical Trials Regulation to minimize the scope for regulatory au-

[8] THE COUNCIL OF EUROPE, *Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: Convention on human rights and biomedicine*, Oviedo, 4 April 1997. Available at: https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164.
[9] THE COUNCIL OF EUROPE, *Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research*, Strasbourg, 25 January 2005. Available at: https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/195.

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tonomy at national level and to make Europe competitive in research, ensuring the production of reliable and robust, high-level scientific data, ensuring patient safety[10].

The Clinical Trials Regulation replaces the Clinical Trials Directive, but although the Regulation entered into force on 16 June 2014 the timing of its application depends on the development of a fully functional EU clinical trials portal and database. The entry into application of the Regulation is currently estimated to occur by the next year. As observed in the preamble of the Regulation, in a clinical trial is necessary to give a primary position to the rights, safety, dignity and well-being of subjects. The new Regulation does not substantially change the rules on the protection of individuals and informed consent introduced by Directive 2001/20/EC; some provisions are reformulated and/or synthesized to facilitate their understanding. Unlike Directive 2001/20/EC, the new Regulation specifically regulates cases where, due to the urgency conditions, it is not possible to obtain free and informed consent beforehand. Article 29 of the Regulation sets forth the general framework for informed consent. Informed consent must include: the nature, objectives, benefits, implications, risks and inconveniences of the clinical trial; the subject's rights and guarantees regarding their protection, in particular his/her right to refuse to participate and the right to withdraw from the clinical trial at any time without any resulting detriment and without having to provide any justification; the conditions under which the clinical trial is to be conducted, including the expected duration of the subject's participation in the clinical trial; the possible treatment alternatives, including follow-up measures, if the participation of the subject in the clinical trial is discontinued. Information must be comprehensive, concise, clear, relevant, and understandable to any person, provided in a prior interview with a member of the investigating team who is appropriately qualified according to the law of the Member State concerned. The article also provides for an interview with an investigator. During the interview, special attention must be paid to the information needs of specific patient populations and of individual subjects, as well as to the methods used to give the information. The Regulation provides for specific attention for vulnerable subjects: article 31 provides particular conditions for clinical trials involving incapacitated subjects; article 32 of the Regulation provides a specific discipline for clinical trials involving minor, specifying that the primary condition for the conduct of a clinical trial involving a minor is the presence of a direct benefit; article 33 provides for specific provisions for pregnant or breastfeeding women participating in clinical trials. Finally, article 34 gives the possibility for Member States to organize a further protection for certain subjects in a situation of institutional or hierarchical dependency likely to inappropriately influence their consent ("persons performing mandatory military service, persons deprived of liberty, persons who, due to a judicial decision, cannot take part in clinical trials, or persons in residential care institutions").

Some Member States, such as Spain and France, have already adopted implementation measures in order to adapt their national legislation to the Regulation (EU) 536/2014. France adopted two decrees on 17 November 2016 in order to adapt its national legislation to the CTR[11]. Spain issued a De-

[10] M. GEHRING, R.S. TAYLOR, M. MELLODY, B. CASTEELS, A. PIAZZI, *Factors influencing clinical trial site selection in Europe: the Survey of Attitudes towards Trial sites in Europe (the SAT-EU Study)*, in *British Medical Journal*, 1.

[11] The first decree (Decree concerning Research Involving Humans No. 1537 of 16 November 2016) focuses on "research involving the human person" and produces many changes, also regarding the role of the national commission for research. The second decree (Decree No. 2016-1538 of 16 November 2016) focuses on the rules regarding contracts for clinical studies for commercial purposes conducted by sponsors in public health

cree to adapt at the future application of CTR and to develop those aspects, which the regulation leaves to national legislation[12].

3. Vaccine trials in European legal framework

Vaccine trials fall within interventional research and they are not "low interventional studies" with minimal risk. Healthy volunteers are the target population for vaccine trials and this requires special carefulness concerning benefit/risk assessment. The fact that such trials involve healthy subjects determines two consequences: a stringent stress on safety both in clinical trials and in clinical practice, and a more rigid regulation concerning informed consent. A rigorous regulatory procedure must therefore be ensured to evaluate quality, efficacy and safety. In vaccine trials, there are: a pre-clinical development, carried out in lab assays and on animals; a clinical development that covers three or four stages. The Clinical development is built on rigorous ethical principles of informed consent from volunteers, with an emphasis on vaccine safety as well as efficacy.

Phase I clinical trials are small-scale trials to assess if a candidate vaccine is safe in humans and what immune response it evokes. Risk assessment in first-in-human trials for vaccine is specifically regulated by the Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products (EMA, Committee for Medicinal Products for Human Use (CHMP) 2007, first revision 2017)[13]. For sponsors, relevant risk assessment for first-inhuman clinical studies means careful design and conduct of studies that reduce potential risk to humans.

Phase II refers to the initial trials examining effectiveness in a limited number of volunteers (usually between 200 and 500); the focus of this phase is vaccine safety, side-effects and the immune response.

Phase III trials are intended for a more complete assessment of safety and effectiveness in the prevention of disease in a large group of people.

Phase IV trial are optional studies that drug companies may conduct after a vaccine is released. This stage aims to detect rare adverse effects as well as to assess long term efficacy.

Within the European Union human vaccines are regulated by European Medicines Agency (EMA)[14].

All manufacturing information including tests for safety, purity, and potency for a particular product is regulated under a Good Manufacturing Practices (GMP) Directive 2003/94/EC[15] and Regulation

establishments. These two decrees complete a government Order dated 17 June 2016, which implemented the law no 2012-300, dated 5 March 2012, on research on human persons. The Ordinance concerning Research Involving Humans (2016/800), dated June 16 2016, amended the Public Health Code.

[12] The RD 1090/2015 provides for that to obtaining and content of informed consent shall follow the provisions of Article 29 of CTR, as well as Articles 8 and 9 of Regulation Law 41/2002, of 14 November. The person participating in the trial, particularly people with special vulnerability will be informed of the access routes to the usual clinical practice for their pathology.

[13] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf (last visited 28/04/2019).

[14] https://www.ema.europa.eu/en (last visited 28/04/2019).

[15] Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (GMP)

(EU) No. 1252/2014[16]. The GMP requires, in general, that medicines are of consistent quality, appropriate for their intended use and that the requirements of the marketing authorisation or clinical trial authorisation are met.
Directive 2001/83/EC and Regulation (EU) No 726/2004[17] constituted the EU regulatory framework for the manufacture, authorization and distribution of veterinary medicinal products. The Regulation (EU) No 726/2004 established a European Medicines Agency that provide regulatory authorities with the mandate to promote and protect public health by authorising the use of safe and effective vaccines and by continuously assessing their benefit and risk profile following the granting of marketing authorisation.
Recently, the regulatory framework has been reviewed by Regulation (EU) 2019/6 of the European Parliament and of the Council on veterinary medicinal products, in order to harmonize the legislative provisions of the Member States. The regulation, which is mandatory in all its elements and directly applicable in all Member States, will enter into force on the twentieth day following its publication in the Official Journal of the European Union and will apply from 28 January 2022.
During the 64th session of the WHO Regional Committee for Europe has been adopted the European Vaccine Action Plan 2015–2020 (EVAP), that imagine a Europe free from vaccine-preventable diseases, where all countries have an equal access to vaccines and immunization services[18].

3.1. Mandatory vaccination and ethical issues: the case of compulsory vaccination in France, Germany, Italy, Spain

The European regulatory framework does not regulate whether vaccines are mandatory or recommended, and the Member States remain free in their decision[19].
However, the EU's role in health policy is limited, because National governments are responsible for deciding how to organise their health service. The European regulatory framework does not regulate whether vaccines are mandatory or recommended[20], and the Member States remain free in their decision. Thus, National Health Services of most European countries have different vaccination systems, different vaccine recommendations and different schedules of vaccine administration.
In the EU, Austria, Cyprus, Denmark, Estonia, Finland, Germany, Ireland, Lithuania, Luxembourg, the Netherlands, Norway (EEA and Schengen), Portugal, Spain, Sweden and the United Kingdom have no obligation to vaccinate The other countries have an obligation to vaccinate with between 1 vaccine (Belgium) and 12 (Latvia). With 11 compulsory vaccines, France would be one of the most constraining countries.

[16] Regulation (EU) No. 1252/2014 of 28 May 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for human use.
[17] Regulation 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
[18] https://www.who.int/ (last visited 28/04/2019).
[19] For knowing vaccine schedules in all countries of the European Union: https://vaccine-schedule.ecdc.europa.eu/ (last visited: 30/04/2019).
[20] https://ec.europa.eu/health/vaccination/overview_en (last visited 28/04/2019).

The Regulation (EC) No 851/2004 of the European Parliament and of the Council of 21 April 2004 establishes a European centre for disease prevention and control. This is an independent agency, a Community source of scientific advice, assistance and expertise from medical, scientific and epidemiological staff acting on behalf of Member States' authorities responsible for human health (article 9). Regulation (EC) No 851/2004[21] mandates the European Centre for Disease Prevention and Control ('ECDC') to support the prevention and control of communicable diseases and foster the exchange of best practices and experience with regard to vaccination programmes[22]. In addition, the ECDC coordinates data collection, validation, analysis and dissemination at EU level, including on vaccination strategies. The European Centre for Disease Prevention and Control (ECDC) established network of experts working in the field of immunisation: Vaccine European New Integrated Collaboration Effort (VENICE)[23], with the objectives of collecting, sharing and disseminating information on national immunization programmes and for improving the overall performance of the immunisation systems in the EU/EEA Member States. The European Centre for Disease Prevention and Control (ECDC), in the *guide Let's talk about prevention. Enhancing childhood vaccination uptake. Public Health Guidance*, 2016, identifies ways to help healthcare providers and encourage all parents to get their children protected by vaccination, particularly those in population groups whose children are currently non and undervaccinated. The guide underlines that vaccines are safe and effective and highlights the balancing of benefits and risks for different diseases. There is no reference to informed consent form but the guidance provides a detailed information on benefits and risks of different vaccinations.

Although vaccination policy is a competence of national authorities, the European Commission supports EU countries to coordinate their policies and programmes[24]. In 2014, the Council of the European Union in the Conclusions on vaccinations as an effective tool in public health[25], invited member states to:

- continue to improve epidemiological surveillance and evaluation of the situation concerning communicable diseases in their territories, including diseases preventable by vaccination;
- continue to improve national vaccination programs and to strengthen national capacity for carrying out evidence-based, cost-effective vaccination, including the introduction of new vaccines where considered appropriate;
- continue to develop plans and standard operating procedures in collaboration with the ECDC and the WHO to ensure a timely and effective response to vaccine-preventable diseases during outbreaks, humanitarian crises and emergencies;

[21] Regulation (EC) No 851/2004 of the European Parliament and of the Council of 21 April 2004 establishing a European Centre for Disease Prevention and Control.

[22] https://ecdc.europa.eu/en/home (last visited 30/04/2019).

[23] VACCINE EUROPEAN NEW INTEGRATED Collaboration Effort (VENICE), *Report on Adult Vaccination Strategies and Vaccine Coverage in Europe,* 2010. Available from: http://venice.cineca.org/.

[24] To learn about vaccine policy of all European countries: https://www.efvv.eu/ (last visited 28/04/2019).

[25] THE COUNCIL OF EUROPE, *Council conclusions on vaccinations as an effective tool in public health*, Brussels, 2014. Available at: https://www.ifa-fiv.org/wp-content/uploads/2015/12/EU-Health-Council-Conclusions-on-Vaccination_Dec-2014.pdf.

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- continue to develop comprehensive and coordinated approaches within vaccination programs, following the Health in All Policies approach creating synergies with broader health policies and pro-actively working with other preventive sectors;
- ensure transparency with regard to the post-marketing evaluations of vaccines and of studies on the impact of vaccination programs in order to provide reliable information for both governments, medicines regulators and manufacturers;
- actively offer appropriate vaccination to population groups considered to be at risk in terms of specific diseases and consider immunization beyond infancy and early childhood by creating vaccination programs with life-long approach;
- work with health professionals on risk communication in order to maximize their role in informed decision making;
- inform the population in order to raise its trust in vaccinations programs, using appropriate tools and communication campaigns also by engaging opinion leaders, civil society and relevant stakeholders (e.g. academia).

As seen in the previous paragraphs, one of the premises for informed consent is voluntariness, but with obligatory vaccination, providing consent could become only a formality or a legal fiction. Therefore, in the case of obligation, voluntariness could be lacking and thus from an ethical and legal perspective, the informed consent is invalid. In the case of a vaccination obligation, a clash between individual's rights and public safety becomes apparent. On the one hand individual autonomy and on the other the need to protect public health protection through obligatory vaccinations[26]. For obligatory vaccinations, there is a paradoxical situation where parents/guardians of children who are to be vaccinated need to sign an informed consent form despite a vaccination obligation. In 2014, the WHO issued a document, titled Considerations regarding consent in vaccinating children and adolescents between 6 and 17 years old, in which it underlines that formal consent can be gathered with opt-in procedure (health authorities inform the parents about the vaccination and written consent from the parent is required to opt-in, i.e. give permission for the older child/adolescent to be vaccinated) or opt-out procedure (a written form is used to allow parents to express non-consent or refusal to vaccination of their child).

Refusing to sign informed consent and therefore refusing to subject the child to vaccination would have legal consequences.

Legal consequences differ from country to country. In some cases, they could be very strong, including pecuniary penalties, difficulty to attend public schools, or even penal consequences for the parents.

The Council of Europe in the Conclusions on vaccinations as an effective tool in public health (2014), recognizes that while vaccination programs are the responsibility of individual Member States and that various vaccination schemes exist in the EU, efforts to improve vaccination coverage may also benefit from cooperation within the EU and from improved synergies with other EU policy areas, having special regard to the most vulnerable populations identified in the different regions and individual Member States of the Union and to increasing mobility.

[26] A. ZAGAJA, *Informed Consent in Obligatory Vaccinations?,* in *Medical Science Monit*or, 2018, 1.

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In France, with regard to vaccines in clinical practice, on June 2017 the Health Minister announced plans to move from three (diphtheria, tetanus and poliomyelitis) to eleven mandatory vaccines, in order to prevent the expansion of certain diseases. These additional eight vaccines – pertussis (whooping cough), Haemophilus influenzae B, hepatitis B, meningococcus C, pneumococcus, measles, rubella and mumps – were only recommended, but Loi n° 2017-1836[27] makes them mandatory since 2018.

Information and consent of parents is always required also if vaccines are mandatory.

Parents who fail to get their children inoculated could face up to six months in prison and a higher fine. Among legal consequences, unvaccinated children in France could be not allowed at any preschool (nursery, daycare, kindergarten) and school grade.

In the German law there are no mandatory vaccinations, but there are strongly recommended vaccinations. Annually the commission for immunization ("Ständige Impfkommission STIKO") publishes its recommendations. Most ministries for health of the 16 federal states assume these without alteration. In exceptional situations the Ministry of Health of the Federal Republic of Germany or the local federal governments are authorized by legal decree to oblige parts of the population to be vaccinated. Provided that an infectious disease with serious clinical end arises and epidemic sprea-ding is estimated (Infectious Diseases Protection Law: Infektionsschutzgesetz - IfSG). The Fundamental Right of being physically unscathed may be limited. Following this law, certain employers are authorized to collect informations about the immune status of employees (e.g. in hospitals) to decide about an occupation or its kind. No legal regulations exist for mandatory vaccination when visiting kindergarten, school or university. If somebody caught an infectious disease or is suspicious of having caught it or of being infected, health institutions may forbid to go to kindergarten or school.

In Italy, ten vaccinations (diphtheria, tetanus, pertussis, poliomyelitis, haemophilus influentiae B, hepatitis B, measles, rubella, varicella and mumps) are mandatory for children since 2017 (Law 119/2017[28]). Parents have to present their vaccination certificates at school and each Region must provide additional recommended vaccinations for free. Schools have to notify the local health agencies (ASL) when parents fail to present the necessary vaccination documents. The decision n. 5/2018 of the Constitutional Court determined that the Law 119/2017 is compliant with the Italian Constitution and that regulatory intervention is not unreasonable, given the current state of epidemiological conditions and scientific knowledge. It aims to protect individual and collective health on the basis of the duty of solidarity in preventing and limiting the spread of certain diseases. The Constitutional Court considered inter alia that all vaccinations made mandatory were already planned and recommended in the national vaccination plans and funded by the State. Furthermore, the shift from a strategy based on persuasion to a compulsory system is considered justified in the light of the gradual decline in vaccination coverage.

Fines up to five hundred euros are imposed for families that fail to vaccinate their children, but penalties must be preceded by the meeting between health authorities and families in order to inform them about the vaccination program. The lack of vaccination implies the exclusion only from nursery

[27] LOI n° 2017-1836 du 30 décembre 2017 de financement de la sécurité sociale pour 2018, JORF n°0305 du 31 décembre 2017.

[28] Italian Law 119/2017 – GU Serie Generale n. 182 del August 5, 2017.

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school and kindergarten. For defaulting of 6-16 year olds will start the recovery process that, in the negative case, culminates with the financial penalty. Information and consent acquisition of parents is however required also if vaccines are mandatory.

In Spanish legislation, vaccines are subject to the general rules for medicinal products for human use. Spain has no mandatory vaccines whilst pressure from health authorities is very high. Vaccine uptake between children is around 95 percent and it is around 40 percent between adults and elderly. Un-vaccinated children in Spain are allowed at any preschool (nursery, daycare, kindergarten) and school grade, but sometimes private schools would not admit unvaccinated children.

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