Special issue

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

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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.

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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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