Ethical Issues Concerning Informed Consent in Translational/Clinical Research and Vaccination Bias and Informed Consent

Aspectos éticos del consentimiento informado en la investigación translacional/clínica y sobre el sesgo o prejuicio en los ensayos clínicos

Alberto García Gómez*
Mirko Daniel Garasic**
María Cubillo Díaz-Valdés***

Abstract

Improving the health literacy of patients in relation to medical practices and research is essential for upholding the principle of respect for autonomy—that is, respecting the patient's ability to make self-governed choices regarding medical interventions or research participation that reflects the patient's beliefs and values. This paper considers the challenges of informed consent (i.e. ethical gaps, barriers, and priority needs) that are unique to cer-

* UNESCO Chair in Bioethics and Human Rights, Rome, Italy: agarcia@unescobiochair.org
** UNESCO Chair in Bioethics and Human Rights, Rome, Italy: mgarasic@unescobiochair.org
*** GSK, Madrid, Spain: maria.x.cubillo@gsk.com
This paper has been elaborated under i-CONSENT project that has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 741856: www.i-consentproject.eu
Received on March 06, 2019. Accepted on March 08, 2019.

tain vulnerable groups, namely preadolescents, adolescents, and pregnant women, with a specific emphasis on how neurobioethical, multicultural and interreligious variables should be taken into account when assessing the appropriateness of the current documents relying on the notion of informed consent. In exploring how we are to improve the process of obtaining informed consent, this contribution pays particular attention to the relevance of bias and privacy in the debate, suggesting new ways of intervening so to reduce the effects of implicit bias.

Key words: Autonomy, Bias, Bioethics, Competence, Informed consent, Vaccination

Introduction

Informed consent process requires of four characteristics to be valid: voluntariness, disclosure, understanding and capacity. Whenever one of these elements is missing, informed consent can be compromised.[1]

Voluntariness, meaning that patients must make the decision to participate without influences or coercion and understanding that they are under no obligation to participate, and if they do, they have the right to withdraw at any time.[2 3]

Disclosure means giving subjects all the relevant and right information about the research, including the risks, potential benefits, nature and other therapeutic alternatives. According to the ethical considerations of the Belmont Report, the following principles are specifically relevant in terms of the existing issues when disclosing the information in the informed consent obtaining process. The principle of autonomy and obligation truth-telling, places disclosure on always providing the complete information to every patient. However, based on the principle of beneficence and the principle of non-maleficence, usually the right approximation to do is only partial disclosure. The principle of justice is not considered here

when analyzing disclosure due to its more limited relevance with this issue.[4] [5] Understanding involves that participants have the ability to comprehend the information and perceive the relevance into their personal lives under reasoned conditions. In other words, appropriate, precise and relevant information should be provided in a language and format that patients fully understand.[6] [7] [8] Capacity in any clinical situation means to be capable of making autonomous decisions and engage into a clinical trial under reasoned deliberations, comparing the risks and benefits of the procedure. A patient needs to have the capacity of self-determination to reflect, decide and consider, when deciding to participate in a clinical trial.[9] [10] Capacity can also be considered as a sliding scale, where not all the decisions need the same level of capacity. In this way, a patient could have the capacity to make a decision but not another. As the importance of the decision increases, and the information given is more specific and accurate, the threshold for considering a patient capable, is also higher. For instance, a life-or-death decision with clinical and technical information, would have a high threshold for capacity and the patient would need to show the required level of ability to reason the decision-making process.[11] [12] In the following section, the role that investigators can have (with their bias) in the obtainment of informed consent will be explored more in detail.

What is bias?

A patient should receive a different care attention relative to his or her specific ethnic group, gender or any other factor. However, there are existing bias, among health care professionals that contribute to health disparities.[13] [14] Bias refers by psychologists as «the negative evaluation of one group and its members relative to another».[15]

A stereotype is «a cognitive structure that contains the perceiver's knowledge beliefs, and expectations about a human

group».[16] The reason why people have stereotypes is because it is a way to simplify the processing and storing of information in a more efficient way in terms of mental energy and time consuming. It has been found that repeated stereotyping leads to a psychological system where consciousness disappears and becomes implicit even when a person is educated in multicultural diversity and has no conscious negative attempts to use their stereotypes.[17]

There are two types of bias: explicit and implicit. The explicit bias is the one that the person has awareness of, and it is associated with deliberative behaviors (e.g. verbal). In the last 50 years, explicit bias in terms of ethnic background or religious beliefs have decreased significantly, being nowadays unacceptable within general society.[18] However, implicit bias, is the one that makes a person acts unintentionally, unconsciously and makes negative associations and judgements without awareness. This kind of implicit bias is persistent and common in the society and it is difficult to control. Implicit bias is normally associated with spontaneous non-verbal behavior such as repeatedly eye contact, sitting away from a person that is not from the same ethnic group as yours, facial expression, and so on. For instance, a person could think that he or she is not racist but then, has unintentionally attitudes that makes him or her act in a prejudiced manner. This non-conscious behavior can influence in the decision-making, health-care professionals and patient's perceptions, and thus, in the quality of care. Implicit racial attitudes have been considered as one of the reasons that may explain why clinicians provide less quality care to patients from a different ethnic background, even when they fully intend to give equal care to everybody.[19] [20] [21] [22] [23]

Recruitment of minorities

Recruitment in research is influenced by several factors that need to be identified in order to improve this process.[24] When talking

about minorities, recruitment for clinical trials have even more barriers and gaps that need to be addressed.[25] Clinical investigators have found it difficult to enroll patients from minorities due to a mistrust relationship, language differences, cultural values and limited access to these populations.[26] In this way, a study that interviewed and look for experiences and perspectives of principal investigators, research staff, referring clinicians and cancer center leaders, showed that multi-level barriers are often faced by minorities that exclude them from being offered an opportunity to participate in a clinical trial. Language discordance was one of the barriers where investigators suggested that the time and effort required with translators could discourage others from even offering the trial to these patients.[27]

One qualitative study performed in London where three clinical research teams were interviewed, showed that there were four themes influential to recruitment: infrastructure, nature of the research, recruiter characteristics and participant characteristics. Focusing on the recruiter characteristics it was noticed that none of the recruiters had received specific training in recruitment. There was a discussion on whether or not this training could affect the recruiter skills or could be useful to improve them. At the end, it was said that an individual's personality was crucial to their recruitment success, meaning that it is an aspect difficult to teach. This suggests again that there is an existing investigator bias that can affect in the recruitment and in consequence in the informed consent obtaining process, as every person is different and thus, can influence in offering or not the participation in a clinical trial to a potential subject. Furthermore, no specific strategies are normally employed for the recruitment of patients from different ethnicities or socio-demographic backgrounds due to the belief that recruiters invite all eligible patients to participate, despite of their background. However, the truth is that recruiters tend to stereotype potential participants based on their previous experiences and choose not to go towards individuals who are otherwise eligible.[28]

A research group from United Kingdom (Centre for Population Health Sciences of the University of Edinburgh; the National Heart & Lung Institute and the Division of Epidemiology of the Imperial College London; and the Medical Research Council (MRC)- Asthma UK Centre for Allergic Mechanisms in Asthma of the Barts and The London School of Medicine and Dentistry) conducted a qualitative case study where a comparison between United States and United Kingdom is done in terms of multiculturalism and multi-ethnic attitudes when recruiting minorities into research. This study is considered particularly relevant in this report, since United States is a reference country with high differences in multi-ethnic and multiculturalism population and also large experience in conducting clinical trials. The study consisted on interviews with 19 researches from UK and 17 from US. Results revealed a wide gap between both countries in terms of policy, attitudes, practices and experiences in relation to the inclusion of ethnic minorities in research. The study showed evidence of UK researchers having a lot of stereotypes and prejudices that were negatively influencing on the recruitment process of ethnic minorities. For instance, one researcher presented ethnic minorities as lacking altruism stating that this population were more focused on their families rather than on society as a whole, describing south Asian people as «a little bit selfish».[29] This gap between US and UK (to an extent linkable to much of Europe) could be explained by the presence in US of the NIH policy in relation to recruitment of women and minorities in clinical trials, that places a responsibility on investigators to ensure that women and members of minorities and their subpopulations are included in all human research not allowing cost as a reason for excluding them and initiate programs and support for outreach efforts to recruit these groups. The absence of such a policy in UK, with the prejudices and stereotypes, contribute to the under-representation of these groups in the clinical trials, and thus, to the existing investigator bias in the informed consent obtaining process.[30] Besides, clinicians can also

find difficulties to provide the information to their patients, because they worry about information being frightening in some cases. For this reason, the investigator's attitude can lead to a biased recruitment selecting patients that they consider «easier» to communicate with.[31]

Researcher influence

Patient decision making process could also be influenced consciously or unconsciously by the investigator. This is so, that various reviews have shown that researcher influence is one of the most provocative variables in patient participation in clinical trials. Patients tend to accept participation when they have a good relationship with the investigator and a reliable relation is built between them. Nevertheless, when patients do not trust their physician, or the physician even discourage them, they are more likely to decline participation.[32] In this way, informed consent is also influenced suggesting that patients are not being objectively informed, and their consent is being influenced by the investigator and other external factors. There is also another kind of bias, called optimism bias which has been seen in patients but also in investigators. This kind of bias is more likely of phase I clinical trials where patients normally do not have another alternative to treatment and accept to participate in research because it's the only choice. In this context, ethical issues arise in whether these patients are consenting without understanding really the trial's purpose or without enough information to make an informed consent decision. For instance, in phase I cancer subjects, optimism bias is commonly found. They hope their own chance of obtaining high medical benefit. Sometimes, even investigators are not immune to therapeutic optimism bias. Despite of their predictions about survival, they show an optimism bias when it comes to patients they know better or they have treated longer. This optimism bias is one

of the most consistent in psychology and its consequences are shown in patients willing to participate and investigators willing to propose the clinical trial.[33]

Limits of Disclosure

Another aspect to consider are the limits of disclosure in informed consent. For now, it has only been discussed the point of view where the investigator's opinion, views, and characteristics can influence on the decision-making process of a potential subject. However, other opinions and reviews state that unless subjects are informed of these investigator's personal characteristics, views and sponsors, their autonomy is being overridden, meaning that subjects could consider the information about researchers important to their decisions. But then, there is also the issue of the investigator's privacy not being respected and the doubt of his or her characteristics not being discriminated.[34]

There are differences in how people understand, accept and react when confronting bad news, or even cultures where giving bad news is not allowed, whereas others think that every kind of information is needed to know, etc. For these inconsistent opinions, disclosure of information should be thought carefully and considering these questions: Who? Where? What? How?[35]

Regarding who should disclose the information, the doctor that best knows the patient should.[36] Where? It should always be disclosed in a private and quiet room, not in the middle of the corridor or in front of other people.[37] What? The relevant and adequate information in each case should be disclosed, whatever is the best for the patient.[38] How? The information should always be disclosed in a sensitive and empathic way, considering also the body language, non-verbal behavior, the wording. Also, patients need to have their time to process the information and a return visit if they wish.[39]

Ethnic/racial implicit bias: neuroscientific approach

We have seen in the previous sections that both neuroscience and cultural background are important variables to take into account when assessing informed consent -and this applies also for what concerns implicit bias. In general, clinical investigators and health care professionals show respect for other cultures and ethnicities, but when applying it to real situations and clinical research, a lot of gaps are identified. This suggests that there is an unconscious bias and stereotyping that lead to the difficulties in communicating, enrollment and informed consent process when other cultures and populations are involved.[40]

It has been seen that when health care professionals have the appropriate time to process the information, enough cognitive resources and the required motivation to avoid bias and prejudices, the care attention they provide is equal within different patients and it is not influenced by implicit bias. However, these implicit attitudes can influence in the behavior and cognitions when the cognitive process capacity is altered by factors such as anxiety, stress, illness, fatigue or cognitive overload. Moreover, in this context, when cognition capacity is loaded too much, people are more likely to stereotype and follow automatic categorizing due to the memory being biased towards implicit attitudes, difficult to override. For this reason, it is important to take this into account in clinical/medical contexts, where it is easy to have situations under stress, time pressure and working memory, that can lead to a cognitive overload, and thus, to a biased behavior.[41] [42]

A plethora of different studies that were conducted in different countries found evidence of existing implicit bias among healthcare professionals, using different testing methods and studying various socio-demographic characteristics. The results showed that the higher the level of implicit bias was, the poorer was the quality of care. There is clear evidence for a relationship between implicit bias and negative effects on patient interaction, but, although this

does not always have to mean a bad treatment, the truth is that, a good relationship between patient and healthcare professional is crucial to provide a good treatment.[43] Another study stated that implicit racial bias in favor of white people over blacks showed less patient-centered attitudes in clinicians, with a less emotional tone and negative communication that rated as poor the care of the visit.[44]

In fact, results have shown that the majority of implicit ethnic bias are favorable to whites over blacks and that these attitudes are different between males or females health care professionals, being stronger for males, which have stronger preferences for whites on explicit and implicit racial attitudes.[45]

Future steps

Implicit bias can be considered as an automatic association between two terms (cue and response). It has been shown that trying to change the association is more effective than trying to change the response itself, because implicit bias is difficult to control and even if physicians are convinced to consciously reduce their perceptions and implicit bias, it is not guaranteed that they have deleted it and they may re-appear again after a while. In this way, there are some findings where admired African Americans are presented to whites and afterwards, implicit bias is reduced. This technique needs to be translated into clinical contexts, but it suggests a possible way to address the bias.[46] [47]

Another possible intervention could be to address the stereotype threat that some patients have which have been shown that may altered patient-researcher communication and thus, increase mistrust. Actions that decrease patient's insights of threat are needed. Self-affirmation is the process where the self-integrity values are affirmed, and it is sometimes used in educational fields to

decrease racial issues. Hence, self-affirmation could help reduce the implicit bias and improve patient-researcher relationship.[48]

Emerging research has shown that explicit cognition can be used to control and mitigate implicit attitudes. Considering this, one of the strategies suggested for health care professionals, is to change the categorization of the patients, focusing on a shared common identity. The health care professional should ask questions about other social identities such as hobbies, interests, occupation, and shifts his or her attention from the patient's ethnicity. This can help to inhibit the implicit negative stereotypes. Moreover, another strategy for reducing the activation of implicit bias can be taking the perspective of the other side, in this case, the minority group. Some findings have shown that when a person imagines to be in the difficult situation of the other side, he or she is more likely to be empathic and adopt a more approving conception as a result. Some workshops that train this, involve viewing a picture of a minority group and write down a story where they spend a day in the life of that patient.[49] There is also evidence that increasing the diversity of health care professionals help to reduce racial and ethnic biases.[50]

Bibliography

1. Bester J, Cole CM, Kodish E. The Limits of Informed Consent for an Overwhelmed Patient: Clinicians' Role in Protecting Patients and Preventing Overwhelm. AMA journal of ethics. 2016;18(9):869.
2. Blair IV, Steiner JF, Havranek EP. Unconscious (implicit) bias and health disparities: where do we go from here? The Permanente Journal. 2011;15(2):71.
3. Cooper L. Overcoming Healthcare Disparities: The role of patient-centered care–College of Public Health and Health Professions celebrating 50 years. Gainesville: University of Florida. 2008.
4. Durant RW, Wenzel JA, Scarinci IC, Paterniti DA, Fouad MN, Hurd TC, et al. Perspectives on barriers and facilitators to minority recruitment for clinical trials among cancer center leaders, investigators, research staff, and referring clinicians: enhancing minority participation in clinical trials (EMPaCT). Cancer. 2014;120 Suppl 7:1097-105.

5. FitzGerald C, Hurst S. Implicit bias in healthcare professionals: a systematic review. BMC medical ethics. 2017;18(1):19.
6. Garasic MD. The Singleton case: enforcing medical treatment to put a person to death. Med Health Care and Philos. 2013;16(4):795.
7. Gorini A, Mazzocco K, Pravettoni G. Decision-Making Process Related to Participation in Phase I Clinical Trials: A Nonsystematic Review of the Existing Evidence. Public health genomics. 2015;18(6):359-65.
8. Hamilton DL, Trolier TK. Stereotypes and stereotyping: An overview of the cognitive approach. 1986.
9. Hardicre J. Valid informed consent in research: An introduction. British Journal of Nursing. 2014;23(11):564-7. Kim EJ, Kim SH. Simplification improves understanding of informed consent information in clinical trials regardless of health literacy level. Clinical Trials. 2015;12(3):232-6.
10. John-Henderson NA. Implicit Cognition. Child and Adolescent Psychiatric Clinics. 2015;24(4):751-63.
11. McCabe MS (ed.) The ethical foundation of informed consent in clinical research. Seminars in oncology nursing; 1999: Elsevier.
12. Newington L, Metcalfe A. Factors influencing recruitment to research: qualitative study of the experiences and perceptions of research teams. BMC medical research methodology. 2014;14(1):10.
13. O'Brien RL, Kosoko-Lasaki O, Cook CT, Kissell J, Peak F, Williams EH. Self-assessment of cultural attitudes and competence of clinical investigators to enhance recruitment and participation of minority populations in research. Journal of the National Medical Association. 2006;98(5):674.
14. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials: a systematic review. Journal of clinical epidemiology. 1999;52(12):1143-56.
15. Sabin DJA, Nosek DBA, Greenwald DAG, Rivara DFP. Physicians' implicit and explicit attitudes about race by MD race, ethnicity, and gender. Journal of Health Care for the Poor and Underserved. 2009;20(3):896.
16. Sheikh A, Halani L, Bhopal R, Netuveli G, Partridge MR, Car J, et al. Facilitating the recruitment of minority ethnic people into research: qualitative case study of South Asians and asthma. PLoS Med. 2009;6(10):e1000148.
17. Steinberg A. Disclosure of information and informed consent: ethical and practical considerations. Journal of child neurology. 2009;24(12):1568-71.
18. Stone J, Moskowitz GB. Nonconscious bias in medical decision making: what can be done to reduce it? Medical education. 2011;45(8):768-76.
19. Tam NT, Huy NT, Thoa LTB, Long NP, Trang NTH, Hirayama K, et al. Participants' understanding of informed consent in clinical trials over three decades: systematic review and meta-analysis. Bulletin of the World Health Organization. 2015;93(3):186-98H.
20. Tham, J, Durante, C, García, A. (eds.) Religious Perspectives on Social Responsibility in Health; 2018: Springer.

21. Van Ryn M, Saha S. Exploring unconscious bias in disparities research and medical education. Jama. 2011;306(9):995-6.
22. Walsh E, Sheridan A. Factors affecting patient participation in clinical trials in Ireland: A narrative review. Contemporary Clinical Trials Communications. 2016;3:23-31.
23. Williamson T. Research, informed consent, and the limits of disclosure. Bioethics. 2001;15(4):341-63.

Referencias bibliográficas

[1] Bester J, Cole CM, Kodish E. The Limits of Informed Consent for an Overwhelmed Patient: Clinicians' Role in Protecting Patients and Preventing Overwhelm. AMA journal of ethics. 2016;18(9):869.
[2] Ibid
[3] Hardicre J. Valid informed consent in research: An introduction. British Journal of Nursing. 2014;23(11):564-7.
[4] Tam NT, Huy NT, Thoa LTB, Long NP, Trang NTH, Hirayama K, et al. Participants' understanding of informed consent in clinical trials over three decades: systematic review and meta-analysis. Bulletin of the World Health Organization. 2015;93(3):186-98H.
[5] Steinberg A. Disclosure of information and informed consent: ethical and practi cal considerations. Journal of child neurology, 2009;24(12):1568-71.
[6] Bester J, op. cit.
[7] Tam NT, op. cit.
[8] Kim EJ, Kim SH. Simplification improves understanding of informed consent information in clinical trials regardless of health literacy level. Clinical Trials. 2015;12(3):232-6.
[9] Bester J, op. cit.
[10] McCabe MS (ed.) The ethical foundation of informed consent in clinical research. Seminars in oncology nursing; 1999: Elsevier.
[11] Bester J, op. cit.
[12] Garasic MD. The Singleton case: enforcing medical treatment to put a person to death. Med Health Care and Philos. 2013;16(4):795.
[13] Blair IV, Steiner JF, Havranek EP. Unconscious (implicit) bias and health disparities: where do we go from here? The Permanente Journal. 2011;15(2):71.
[14] FitzGerald C, Hurst S. Implicit bias in healthcare professionals: a systematic review. BMC medical ethics. 2017;18(1):19.
[15] Blair IV, op. cit.
[16] Hamilton DL, Trolier TK. Stereotypes and stereotyping: An overview of the cognitive approach. 1986.

[17] Stone J, Moskowitz GB. Non conscious bias in medical decision making: what can be done to reduce it? Medical education. 2011;45(8):768-76
[18] Ver por ejemplo: Tham, J, Durante, C, García, A. (eds.) Religious Perspectives on Social Responsibility in Health; 2018: Springer.
[19] Blair IV, op. cit.
[20] FitzGerald C, op. cit.
[21] Stone J, Moskowitz GB. Non conscious bias in medical decision making: what can be done to reduce it? Medical education. 2011;45(8):768-76.
[22] Sabin DJA, Nosek DBA, Greenwald DAG, Rivara DFP. Physicians' implicit and explicit attitudes about race by MD race, ethnicity, and gender. Journal of Health Care for the Poor and Underserved. 2009;20(3):896.
[23] Van Ryn M, Saha S. Exploring unconscious bias in disparities research and medical education. Jama. 2011;306(9):995-6.
[24] Newington L, Metcalfe A. Factors influencing recruitment to research: qualitative study of the experiences and perceptions of research teams. BMC medical research methodology. 2014;14(1):10.
[25] Durant RW, Wenzel JA, Scarinci IC, Paterniti DA, Fouad MN, Hurd TC, et al. Perspectives on barriers and facilitators to minority recruitment for clinical trials among cancer center leaders, investigators, research staff, and referring clinicians: enhancing minority participation in clinical trials (EMPaCT). Cancer. 2014;120 Suppl 7:1097-105.
[26] O'Brien RL, Kosoko-Lasaki O, Cook CT, Kissell J, Peak F, Williams EH. Self-assessment of cultural attitudes and competence of clinical investigators to enhance recruitment and participation of minority populations in research. Journal of the National Medical Association. 2006;98(5):674.
[27] Durant RW, op. cit.
[28] Newington L, op. cit.
[29] Sheikh A, Halani L, Bhopal R, Netuveli G, Partridge MR, Car J, et al. Facilitating the recruitment of minority ethnic people into research: qualitative case study of South Asians and asthma. PLoS Med. 2009;6(10):e1000148.
[30] Ibid.
[31] Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials: a systematic review. Journal of clinical epidemiology. 1999;52(12):1143-56.
[32] Walsh E, Sheridan A. Factors affecting patient participation in clinical trials in Ireland: A narrative review. Contemporary Clinical Trials Communications. 2016;3:23-31.
[33] Gorini A, Mazzocco K, Pravettoni G. Decision-Making Process Related to Participation in Phase I Clinical Trials: A Nonsystematic Review of the Existing Evidence. Public health genomics. 2015;18(6):359-65.
[34] Williamson T. Research, informed consent, and the limits of disclosure. Bioethics. 2001;15(4):341-63.
[35] Steinberg A. Disclosure of information and informed consent: ethical and practical considerations. Journal of child neurology. 2009;24(12):1568-71.

[36] Ibid.
[37] Ibid.
[38] Ibid.
[39] Ibid.
[40] O'Brien RL, op. cit.
[41] Stone J, op. cit.
[42] Van Ryn M, op. cit.
[43] FitzGerald C, op. cit.
[44] Cooper L. Overcoming Healthcare Disparities: The role of patient-centered care –College of Public Health and Health Professions celebrating 50 years. Gainesville: University of Florida. 2008.
[45] Sabin DJA, op. cit.
[46] Blair IV, op. cit.
[47] John-Henderson NA. Implicit Cognition. Child and Adolescent Psychiatric Clinics. 2015;24(4):751-63.
[48] Blair IV, op. cit.
[49] Stone J, op. cit.
[50] John-Henderson NA, op. cit.