

*The ethics of informed consent in novel treatment including a gender perspective*

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<sup>1</sup> R = Report, DEM = Demonstrator, prototype, DEC = Websites, press & media actions, videos, OTHER = Software, technical diagram, etc.

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## Executive Summary

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 report provides a full review of informed consent challenges (i.e. ethical gaps, barriers, and priority needs) that are unique to certain 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 obtain informed consent, we will also highlight the relevance of bias and privacy in the debate. The objective is to offer recommendations on how these gaps, barriers, and challenges may be solved or avoided in the future. There are two categories of challenges. The first category is comprised of challenges that are patient-centered, which prevent a research subject from fully comprehending the disclosed information. The second category is comprised of challenges that are process-centered, which are procedural barriers that prevent obtaining truly informed consent from prospective patients. The types of recommendations explored for solving or avoiding these two forms of barriers in the context of research and vaccine administration include: 1) understanding more in depth the potential information derived from progress in neuroscience; 2) taking into account the role of religion and non-Western cultures in relation to a person-centered way of conceptualizing informed consent; 3) improving the readability and design of consent forms; 4) identifying the cultural and other bias of both the patient and the doctor/researcher; 5) evaluating the role of privacy in the collection of sensitive data connected to informed consent; 6) incorporating education-specific strategies to improve patients’ or participants’ understanding of consent information; 7) initiating discussion of meningitis, HPV, or RSV immunization and clearly explaining the benefits of infection prevention through immunization; 8) inviting questions at every step of the consent process; 9) acknowledging and addressing discrimination based on age and gender; 10) obtaining consent from legal representatives (in the case of children or pregnant women limited by mental defects or disorders); 11) protecting the privacy of participants enrolled in vaccine-related research; 12) acknowledging patients’ or participants’ own experiences with meningitis, RSV, and/or HPV infection; 13) implementing procedures to assess patients’ or participants’ capacity to consent; 14) supporting parenting strategies and lifestyle practices that reduce and reverse predisposing risk factors to meningitis, RSV, and HPV infection; 15) adopting individualized approaches to promote health protective behaviours (tailoring the consent process to reduce concerns relating to vaccine cost, pain, safety, side effects, perceived appropriateness to lifestyle, and/or need for multiple doses); and 16) implementing a dynamic informed consent model with participant control, accompanied by appropriate privacy safeguards.

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## 1. Introduction

This report will identify the ethical gaps, barriers and challenges currently present in obtaining informed consent in biomedical research, prior to the administration of vaccines, and during translational/clinical vaccine research involving human participants. This report is divided into eight parts. First, a general understanding of the notion of informed consent will be introduced, so to contextualize the current and future development of the informed consent process. In doing so, the report will take a closer look at both the neurobioethical and multicultural/interreligious elements that the notion of informed consent brings into the two fields of research, underlining how and where we need to re-address our attention in the shaping of new guidelines. Subsequently, the report will focus on the role of cultural bias and privacy in biomedical research, putting forward some additional concerns related to informed consent that have ethical relevance. Finally, the report will discuss the universal principles regarding informed consent in general, and which are applicable both prior to the administration of vaccines, and during translational/clinical vaccine research involving human participants. In particular, attention will be given to preadolescents, adolescents, and pregnant women, with specific relevance to cases of the novel meningitis vaccines, the Respiratory Syncytial Virus (RSV), and the Human Papilloma Virus (HPV). By identifying the ethical gaps, barriers and challenges that apply to these specific vulnerable population, in these particular vaccination cases, this report will be able to highlight some specific principles of informed consent to safeguard the priority and specific needs of these vulnerable populations. Based on the general principles identified in the first part of the document and the specific principles identified in the second part, the report will then present in final part some recommendations for formulating future consent forms, interacting with vulnerable populations and obtaining informed consent for vaccination. These recommendations will highlight the priority needs that should be addressed in the context of informed consent for biomedical research, the administration of vaccines and for the translational/clinical vaccine research in general, with specific emphasis on vaccination cases involving young people and pregnant women.

### 1.1. Informed Consent in Biomedical Research

Since the end of WWII, informed consent has gained constant centrality and relevance in the building of guidelines, documents and regulations for biomedical research, clinical research and research ethics. Due to the atrocities committed by humans on other human beings, the international community agreed in guaranteeing an always more powerful role to the patient/subject's autonomy and self-determination in making choices freely -so to ensure a moral legitimacy to all the research results and practices derived from a procedure following the protocol of an informed consent form. Human subjects had to be granted their right to - potentially- refuse to participate in research. Hence, each program involving human subjects had to guarantee that informed consent was obtained prior to any clinical involvement of the human subject.



Another dimension that has been at the groundwork of the construction of the currently implemented informed consent forms in Western countries is a more socio-political one, and it relates more directly to justice. The implicit and explicit statement made by our current regulations and guidelines is the following: no research can promise enough improvement for society to justify the suppression of individual rights and autonomy. Hence, a standard utilitarian approach that will see as justifiable the suffering of a few for the benefit of the many is not -and will not- be tolerated as morally acceptable. And the institutionalization of informed consent as the standardized way of approaching the participation of human subject in biomedical research is the safety net against such a threat.

Of absolute importance, is also the role that experts have in evaluating the scientific validity and ethical permissibility of research. In fact, clinical research requires that either an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) -hence internal to the company or institute- would, through a review process, guarantee for the ethical soundness of the proposed research. The IEC/IRB has to approve the research for its scientific potential as well as for its ethical approach, affirming clearly that the safety, well-being and rights of the human subjects involved are not at risk.<sup>3 4 5 6</sup>

The process of informed consent is normally defined as the one through which patients understand and learn more about the benefits, purpose and clinical risks of a medical procedure and then agree to undergo it. This can include medical experimentation, clinical trials as well as more standard medical procedures (such as blood transfusion) that carry with them always some risks. The informed consent process normally requires the signature of a form by the patient or the proxy confirming the understanding of the benefits and risks of the intervention.

## 1.2. Informed Consent as a Process

As mentioned by Umesh Chandra Gupta in his article titled 'Informed consent in clinical research: Revisiting few concepts and areas': "When a subject has given the consent to research participation, the process of informed consent does not end here and obtaining informed consent in clinical research, rather than one-time event, is in fact a dynamic and ongoing process. Also, providing consent does not obligate the study subjects to stay in the research till its completion. Study participants always have the right to withdraw their consent

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<sup>3</sup> ICH harmonised tripartite guideline: Guideline for good clinical practice, E6 (R1) [Accessed 12 March 2018]. Available from: [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6\\_R1/Step4/E6\\_R1\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1_Guideline.pdf).

<sup>4</sup> Good clinical practices for clinical research in India. [Accessed 12 March 2018]. Available from: <http://cdsco.nic.in/html/GCP1.html>.

<sup>5</sup> WMA declaration of Helsinki-Ethical principles for medical research involving human subjects. [Accessed 12 March 2018]. Available from: <http://www.wma.net/en/30publications/10policies/b3/index.html>.

<sup>6</sup> The Belmont report: Ethical principles and guidelines for the protection of human subjects of research. [Accessed 12 March 2018]. Available from: <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>.

at any time during the study. Continued consent refers to obtaining the consent repeatedly from the subjects, whenever required or indicated during the course of conduct of the study, even if the initial consent was obtained at the study entry. Once the informed consent is obtained from a study subject, obtaining re-consent of the subject is further an important ethical aspect in clinical research in terms of “when re-consent should be obtained”. Even after obtaining informed consent from the study subjects, certain situations may be encountered requiring informed consent again to be obtained.”<sup>7</sup>

Given that the researchers have the moral obligation to protect the rights of the human subjects involved in the studies, it is imperative that any relevant information that could determine a readjustment of the decision of the subjects to participate should be given to them as soon as available. Such information can be categorized in four main groups. A) Information that could change the decision of the IEC/IRB. In this case the information would more relevantly be shared with the “third party” ethics committee but obviously for and with the subject as well. B) Information that could affect the predisposition of the subjects to continue with their participation in the research. Situations where data confirm that they have no real chance to gain benefits from continuing the procedure. C) Information that could damage the well-being, safety and rights of the subjects. For example, the discovery of unforeseen risks with procedure. D) Information that could alter the methodology or procedures previously agreed on. For instance, the increase of dosage from once a month to once a week. Not only researchers have duties, but also subjects have rights to ask for clarifications, raise doubts and interrupt the procedure (even if resulting from a previously signed informed consent form). That is why the repetitive status of obtaining informed consent becomes important<sup>8 9 10</sup> for both agents involved in the studies: on the one hand the subjects are guaranteed a constant supervision and can always withdraw their consent and on the other hand the researcher can track their commitment to respect the subjects by sharing all the relevant information with regular intervals.

Aside from the conscious awareness of new data and information that researchers could encounter, there are also other possible scenarios in which a resubmission of informed consent form might be necessary after an initial agreement.<sup>11</sup>

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<sup>7</sup> Gupta, U. C. (2013). Informed consent in clinical research: Revisiting few concepts and areas. *Perspectives in Clinical Research*, 4(1), 26–32. <http://doi.org/10.4103/2229-3485.106373>

<sup>8</sup> ICH harmonised tripartite guideline: Guideline for good clinical practice, E6 (R1) [Accessed 12 March 2018]. Available from: [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6\\_R1/Step4/E6\\_R1\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1_Guideline.pdf).

<sup>9</sup> Good clinical practices for clinical research in India. [Accessed 12 March 2018]. Available from: <http://cdsco.nic.in/html/GCP1.html>.

<sup>10</sup> National cancer institute: A guide to understanding informed consent. [Accessed 12 March 2018]. Available from: <http://www.cancer.gov/clinicaltrials/patientsafety/informed-consent-guide/page1/AllPages>.

<sup>11</sup> Gupta UC. GCP and clinical research: A managerial approach. 1st ed. New Delhi: Viva Books Private Limited; 2011. pp. 50–68.

Scenarios like these ones could take place because of a mistake made in the process of obtaining informed consent from the subject. These cases are more likely to happen in contexts of biomedical trials, where there is a high level of regulation and the tolerance towards these kind of error is minimal. As already mentioned in fact, the given guidelines are there to protect the well-being and rights of the subjects, so the moment some mistakes in the process are found, they call for extreme attention. The way to categorize an error in the process of acquisition of informed consent is quite linear: if it affects any of the key elements at the base of valid informed consent (they will be expanded later in the report) -namely voluntariness, disclosure, understanding and capacity- then the error is to be considered too incisive on the judgement reached by the subject, and calls for resubmission of her or his consent. Among other examples, certainly one could be represented by a wrong or inappropriate translation of the informed consent form to the subjects (in this particular case to be expected to not share the same linguistic/cultural background as the researchers). As it will be stressed in chapter 3, language and cultural barriers can represent an impediment for effective communication between patient/doctor and subject/researcher to reach scientific valid results. In a multicultural world such as ours, this aspect is very relevant indeed.

Another important aspect, that will be taken into consideration more in detail in the next chapter, is that of the presence of capacity in patient with mental impairment (be it because of default conditions that jeopardize their autonomy constantly or because a gradual loss of their autonomy to provide valid consent due to a medical condition). The specificity of alternate agencies in a human subject involved in biomedical research (competent vs incompetent) requires an ongoing reaffirmation of the informed consent, especially in research that are extended in time. The issue of resubmitting one's informed consent form in more than one moment in time will also be considered later in the report, but -given that it overlaps with some of the content of our next chapter but at the same time goes beyond the scope of this project- it is worthy to mention that Gupta and others<sup>12 13</sup> have provided a valuable review on the ethical issues related to informed consent in psychiatry clinical research. It is important to stress that, as stated in the beginning, this report should be read with this crucial definition in mind: informed consent is a process. With all the above considerations, we should gradually enter into the specific aspects that need to be analyzed so to gather new, valuable information and understanding on the topic.

### **1.3. Issues of Ethics of Informed Consent in Clinical Trials**

Informed consent is described in ethical codes and regulations for human subject's research. International guidelines define research as a systematic activity designed to develop or contribute to generalizable knowledge. The first set of ethics rules for research in humans

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<sup>12</sup> Gupta UC, Kharawala S. Informed consent in psychiatry clinical research: a conceptual review of issues, challenges and recommendations. *Perspect Clin Res.* 2012; 3:8–15.

<sup>13</sup> Gupta UC. Informed consent in psychiatry clinical research Concepts, issues, challenges, and recommendations. 1st ed. Saarbrücken, Germany: LAP Lambert Academic Publishing; 2012. pp. 56–64.

formulated by the international medical community was established in 1964 by the World Medical Association (WMA), in the Declaration of Helsinki (Declaration).<sup>14</sup> The aim of this Declaration is to define how to conduct ethical human research, with a focus on clinical trials. For instance, medical research involving human participants must conform to generally accepted scientific principles, based on a thorough knowledge of the scientific literature and other relevant sources of information, and performed with an adequate laboratory and, when appropriate, animal experimentation. Indeed, clinical trials should be described in a clear, detailed protocol. The investigator should utilize qualified individuals throughout all stages of the trial process, from designing the protocol and case report forms and planning the analysis to analyzing and preparing interim and final clinical trial reports.<sup>15</sup> The declaration is unequivocal about protecting the dignity, safety, and rights of research participants. Concerning health, clinical trials have uncertainties in relation to both risks and potential benefits. Determining risk-benefit balance is one of most difficult ethical issues to be addressed in the informed consent. In general terms, for research involving more than minimal risk of harm to participants, the investigator must guarantee that the potential benefit predominates the risk of harm: "In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests. [...] Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects."<sup>16</sup> (Declaration of Helsinki). Generally, the risk of harm and possible benefits are extremely relative to the phase of a clinical trial, the type of therapeutic agent investigated, the illness under trial, the best treatment in progress and the standard of care given. The type and number of clinical investigations and number of participants can all also change things. The harm of a clinical trial is generally fixed by the menaces of adverse reactions. Evaluations of risk of trials are determined from both in advance clinical experiences and pre-clinical experiences. It is obligatory that all foregoing experiences in using the agent are summarized and defined in the trial protocol. It is the role of the Investigator to establish if a clinical trial has an ethically satisfying risk-benefit balance, though potential participants to determine whether to participate or not. The investigator must make sure that the clinical trial is fitly planned and directed, while at the same time verifying that humans are not exposed to excessive risks. Potential risk to humans is ordinarily understood as a risk evaluation in relation to anticipated benefits, to subjects, and the importance of the knowledge that may reasonably be expected to result. Either the level of potential risk and the chance of its case are considered, and at the same time they produce an estimate of the global risk of harm. Clinical trials with a risk of harm greater than minimum level should be submit to an advanced degree of ethics review.

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<sup>14</sup> WMA declaration of Helsinki-Ethical principles for medical research involving human subjects. [Accessed 12 March 2018]. Available from:<http://www.wma.net/en/30publications/10policies/b3/index.html> .

<sup>15</sup> WMA declaration of Helsinki-Ethical principles for medical research involving human subjects. [Accessed 12 March 2018]. Available from:<http://www.wma.net/en/30publications/10policies/b3/index.html> .

<sup>16</sup> WMA declaration of Helsinki-Ethical principles for medical research involving human subjects. [Accessed 12 March 2018]. Available from:<http://www.wma.net/en/30publications/10policies/b3/index.html> .

The notion of minimal risk increases peculiar questions, especially when new agent products are studied in interventional studies. This research frequently imply doubts about the exact vastness and type of harm that can happen, which restricts a stable recognition of risk of harm. Many times it is difficult to predict the accurate kind and importance of the benefits and harm of a trial clinic project; therefore, a need for safety monitoring. Risks of harm should be evaluated consistently, considering physical, social (how others might treat them as a result of their participation in a study) and psychological (possibility that research participants will become emotionally distressed, fearful or anxious as a result of their participation) harm, or economic risks (possibility that research participants will be required to incur additional financial costs as a result of their participation in a study) . Likewise, potential benefits should be valued systematically in perspective of physical, psychological and economic benefit. Finally, the rating should define either the importance and the duration of the potential risk of harm as well as the benefits. The potential benefits are always for the contribute to knowledge that can be applied to good of society. But a new therapeutic product is a test article, not acknowledged medical therapy, so the beneficial utility for participants is dubious. Most participants become involved in clinical trials because they need treatment. The investigator must guarantee the procedures for engagement and informed consent emphasizing the differences between research and standard clinical care that participants might differently receive. The participants may benefit by, for example, being observed and followed up more often than might otherwise be the case, which is particularly beneficial for those in places with low health care. However, such trials need to be carefully evaluated in terms of risks because individuals can be forced or excessively influenced to enroll for the benefits of free examination. The voluntary aspect is prominent, because it is the participants who decide to take part in agreement with his or her own preferences and desires. To preserve the voluntary space, participants should be free to retreat from the research at any time. Investigators members must be conscious of the policy used for participant recruitment, that is the person who having control on the recruitment, when the participants will be approached and how they will be approached. Those are critical elements both assuring or mining the voluntary factor. Undue influence may occur when potential participants are approached by persons in a position of authority. Any relation of addiction – enclosing even between a physician and a participant – may produce an unjustified influence. The financial indemnity for participation is specially connected to the lost time of participation. Indemnity should not be so inviting as to compose a captivating incentive to take higher risks than would other be the case. This is especially true for participants in first phases of clinical trials. The choice to participate in a clinical trial requires evaluating the risk of harm and potential benefits prior to according to participate. Either the informed consent discussion between the investigator and the participants, and the written informed consent document should incorporate explications of significant issues. These comprehend, for example, that the trial entails research; study treatments or interventions; expected duration of subject participation; what is done and when; stopping rules or discontinuation criteria. Overall, process trials should start only after written informed consent has been well documented.

Conventionally informed consent is thought to be in terms of the documents signed and dated by participants, setting forth the purpose, benefits, risks and other study information necessary to allow the participants to make an informed and voluntary decision to participate in the clinical study.

In the Ethical issues in Patient Safety Research is written that: “The informed consent document must provide the requirement of obtaining individual informed consent from patients:

- The research does not directly inform or alter the individual patients’ therapeutic or medical treatment plans; and
- Risks posed to patients by the research are minimal; and
- The research could not practically be carried out if individual informed consent were required; and
- The privacy and confidentiality or anonymity of individual patients are assured.”<sup>17</sup>

With this scheme in mind, the analysis will now move to the specific aspects related to informed consent considered by this report, starting with connection between informed consent and neurobioethics.

## 2. A Neurobioethical Perspective on Informed Consent<sup>18</sup>

### 2.1 Informed consent and neurobioethics

Elisabetta Sirgiovanni gives us a detailed description of the interconnection between neurobioethics and informed consent: “since its beginning, the neuroethical debate has recognized informed consent as a crucial notion about which to interrogate neurocognitive sciences for more empirically-driven reformulations in (bio)ethics.”<sup>19 20</sup> The importance of informed consent in medical practice and research is such that nowadays its lack is universally recognized to be one of the worst forms of negligence, malpractice or tort by healthcare professionals. With the goals of protecting the patients from harm, paternalistic judgments, or external interests, informed consent is considered an essential requirement for prevention of

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<sup>17</sup> Hurst, Samia, et al. & World Health Organization. *Ethical issues in Patient Safety Research: Interpreting existing guidance*. Genève: World Health Organization, 2013.

<sup>18</sup> This chapter is the result of an international workshop held on December 13 2017 at Ateneo Pontificio Regina Apostolorum in Rome -where we gathered a number of experts in the field of neurobioethics so to include their knowledge in the report. Experts were invited to give their insights and comments about a working document with some keys questions to be addressed. The working document was elaborated based on a narrative review of relevant and focused scientific literature. In addition, experts received reading material ahead of the workshop. The contributors where then asked to send a written paper in which they responded to some of the points, while addressing those and other issues in the discussions occurred during the workshop.

<sup>19</sup> Northoff, G. (2006). Neuroscience of decision making and informed consent: an investigation in neuroethics. *Journal of Medical Ethics*, 32(2), 70-73.

<sup>20</sup> Northoff G. (2009). What is neuroethics? Empirical and theoretical neuroethics. *Current Opinion in Psychiatry*, 22(6): 565-9.

the patient's personal autonomy against dominance and abusive conduct.<sup>21</sup> However, informed consent is a protection for medical doctors as well,<sup>22</sup> as it is their own interest to disclose enough about the risks and benefits of proposed treatments to improve prognoses and to insure fiduciary responsibilities, also in order to avoid future legal action. Both pivotal and critical principle in medical ethics and research ethics, informed consent is tied to philosophical views about moral agency and autonomy, and it is an intrinsically interdisciplinary notion.<sup>23 24</sup> In fact, the voluntary choice to give consent to medical treatment or to participate in a research study requires a present state of individual autonomy, or a series of conditions according to which the patient's decisions are thought to be "her own". This implies both the patient's *capacity* of self-government (i.e. moral agency) and the *right* to be free to exercise such self-government (i.e. legal autonomy). These notions are and should be derived by empirical descriptions and normative formulations in other fields beyond moral philosophy, from cognitive neurosciences to law."<sup>25</sup>

On the one hand, recent progress in neuroscience has led to the demand for what has been called "neurobioethics". As considered by Alberto Carrara,<sup>26</sup> one of the most exciting aspects of this field is that neuroscience will allow us to reveal the psychological and neuronal processes involved in ethically relevant notions. For example, recent imaging studies investigating the neuronal correlates of moral judgement show that moral judgement activates specific regions in the brain such as the medial prefrontal cortex. This raises several questions: does moral judgement consist of nothing else but the activation of certain regions of the brain? Do we have to consider moral judgement as being brain based? Do we have to replace what we so far have called moral decisions by particular types of brain activity? As a result, it seems clear, that such speculations need to be addressed and taken abundantly into consideration by any project that wants to analyze convincingly the debate on informed consent -especially for what concerns regulating future guidelines on the topic. As development in neuroscience is revealing us the neuronal correlates of complex psychological processes involved in ethically relevant notions such as informed consent, it is scientifically and ethically mandatory to include such considerations here. Among others, neuroscientist, psychiatrist and philosopher Northoff,<sup>27</sup> affirms that we can understand the concept of informed consent in a multidimensional way as a circular and interdependent dialogue that involves both complex psychophysiological processes of decision making and normative values reflecting the respective sociocultural

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<sup>21</sup> Eyal N. (2011) Informed consent. In: Zalta E.N., Stanford encyclopedia of philosophy, available online: <https://plato.stanford.edu/entries/informed-consent/>.

<sup>22</sup> Paterick TJ, Carson GV, Allen MC, Paterick TE, Medical informed consent: general considerations for physicians, Mayo Clin Proc. 2008 Mar;83(3):313-9. doi: 10.4065/83.3.313.

<sup>23</sup> Del Carmen M.G., Joffe S. (2005). Informed consent for medical treatment and research: a review. The Oncologist, 10: 636–641.

<sup>24</sup> Felsen G., Reinen P.B. (2011). How the neuroscience of decision-making informs our conception of autonomy. AJOB Neuroscience, 2(3): 3-14.

<sup>25</sup> Sirgiovanni, E. 2017. I-Consent December Workshop. *Forthcoming*

<sup>26</sup> Carrara, A. 2017. I-Consent December Workshop. *Forthcoming*

<sup>27</sup> Northoff, G. (2006). Neuroscience of decision making and informed consent: an investigation in neuroethics. Journal of Medical Ethics, 32(2), 70-73.



context. The neurobioethical variables involved in the decision-making process should be taken into consideration before proceeding into a more in-depth analysis of the cultural ones in the next chapter. Landi,<sup>28</sup> Marazziti<sup>29</sup> and others characterize informed consent as a complex human phenomenon that can be interpreted according to a multidimensional model of both perceptive, affective, emotional, motivational, and cognitive processes. Informed consent involves human dimensions such as:

- awareness of suffering from an illness;
- self-examination and self-knowledge of understanding the cause and source of specific symptoms;
- recognizing the need for a specific treatment for which the person has to give his/her consent.

On the other hand, Informed consent presupposes a level of individual autonomy that can be challenged by development in neuroscience. Should we -as some scholar suggest while interpreting some of the findings that neuroscience have produced in the last decade- accept that free will does not exist? If so, what would be the consequences that such an acceptance would entail for our currently widely accepted notion of autonomy?

In order to enter the specificity of the debates related to the application of the notion of autonomy and informed consent in clinical and translational research, first there is a need to construct a more general framework within which one can move.

Out of a number of definitions of autonomy,<sup>30</sup> of particular relevance for the idea behind the construction of the notion of informed consent (and its affirmation in medical care and clinical research) are the following:

### 2.1.1. Autonomy as freedom to have one's will respected

The libertarian view of autonomy that is understood as the freedom to choose between different options without external restrictions or obligations seems to correspond significantly to Isaiah Berlin's concept of negative freedom,<sup>31</sup> which -we should not forget- evolved out of Mill's concept of liberty and thus came to be defined as "libertarian". In such cases, respect for autonomy would be limited to the acceptance of the patient's will without any evaluation of the validity of such a choice. Enforced treatment thus could not be justified where the patient is considered to be sufficiently competent to give -or deny- her permission for the application of a particular healthcare procedure. The acceptance of respect for the patient's autonomy

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<sup>28</sup> Landi, P., Marazziti, D., Rutigliano, G., Dell'Osso, L. (2016). Insight in Psychiatry and Neurology: State of the Art, and Hypotheses. *Harv Rev Psychiatry*. 24(3), 214-28.

<sup>29</sup> Marazziti, D., Dell'Osso, L., Di Nasso, E., Pfanner, C., Presta, S., Mungai, F., Cassano, G.B. (2002). Insight in obsessive-compulsive disorder: a study of an Italian sample. *Eur Psychiatry*. 17(7), 407-10.

<sup>30</sup> Garasic, M.D., Guantanamo and other cases of enforced medical treatment -a biopolitical analysis, Springer, 2015.

<sup>31</sup> Berlin, I., *"Two concepts of Liberty"*, in *Four Essays on Liberty*, OUP, 2002, p.118-172.



does not, and should not, assume an automatic responsive duty on the part of doctors involved in the patient's treatment.

### 2.1.2. Autonomy as substantive-procedural conception

In her book *Understanding Eating Disorders* Simona Giordano underlines further the link made between autonomy and practical rationality, pointing out its limits especially in relation to mentally ill patients. This group is especially at risk of not being eligible to express their will due to the presence in wider society of an embedded acceptance of notions described by John Rawls (ideal rationality)<sup>32</sup> and Danny Scoccia (social acceptability).<sup>33</sup> However, as John Harris<sup>34</sup> points out, in situations such as that of anorexic patients, not considered "genuinely autonomous", we would end up tolerating the paradoxical situation of claiming to respect them by not respecting what they really want. Clearly, this premise of "genuine autonomy" risks establishing a biased approach to what is justifiable. Giordano writes: "a substantive conception of autonomy, in fact, leads to the justification of an authoritarian attitude towards the patient and disregard for patient autonomy."<sup>35</sup> An alternative to this controversial conception is a procedural (or formal) conception of autonomy, and it is this that constitutes the legal approach to decision-making capacity in the UK, as defended by numerous liberal philosophers.<sup>36</sup> The key aspect is that in this latter conception, decision-making capacity is not dependent on the status<sup>37</sup> of the patient but is instead a decision-relative concept.<sup>38</sup>

### 2.1.3. Autonomy as consistency with past decisions

In his *Life's Dominion*, Ronald Dworkin affirms that a key aspect of defining a choice as autonomous is the consideration of its consistency with past choices made by the same individual. The centrality of personal integrity, or identity, is what is most important in this model of autonomy. Respecting one's autonomy should always take into account the need on the part of the authorities to ensure that individuals -where established to be competent- be allowed the chance to live their lives in accordance with their "distinctive sense of their own character."<sup>39</sup> A very important development of this view was made by George Agich,<sup>40</sup> who, still giving major importance to the role of one's identity in assigning the level of respect for one's autonomy, expanded the entitlement to affirm an individual's choice to third parties sufficiently capable of representing (in Dworkian terminology) the individual's character. To give a practical example, the surrogate decision-maker of a patient in a vegetative state should be entitled to

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<sup>32</sup> Rawls, J., *A Theory of Justice*, OUP, 1999, p.248-250.

<sup>33</sup> Scoccia, D., "Paternalism and Respect for Autonomy", *Ethics*, Vol.100, Issue 2, 1989-1990, p.318-334.

<sup>34</sup> Harris, J., *The Value of Life*, Routledge, 1994, p.194.

<sup>35</sup> Giordano, S., *Understanding Eating Disorders*, OUP, 2005, p.48

<sup>36</sup> See for example: Engelhardt, T., *The Foundation of Bioethics*, 2<sup>nd</sup> edition, OUP, 1996, and "The many faces of autonomy", *Health Care Annual*, 9, 2003.

<sup>37</sup> McHale, J., and Fox, M., *Health Care Law*, London, Maxwell, 1997, p.280-281.

<sup>38</sup> Harris, J., *The Value of Life*, Op. Cit, chapter 10.

<sup>39</sup> Dworkin, R., *Life's Dominion*, Harper Collins, 1993, p.222-229.

<sup>40</sup> Agich, G., *Dependence and autonomy in the old age: An ethical framework for long-term care*, CUP, 2003.

decide to end artificial feeding as long as she would be able to demonstrate that this decision would be in line with the values expressed by the patient over the course of her life.

#### 2.1.4. Autonomy as capacity to choose validly

A final contrasting way of defining autonomy places the emphasis not on the values of the patient as in the conception outlined above, but rather on the decision-making process. In order to establish the level of autonomy thus, we need to ensure that the patient is capable of processing the information given, reflecting on it and reaching a “reasonable” conclusion. What has to be established, in other words, is whether the patient is competent or not. This approach has produced legislation such as the Mental Capacity Act 2005<sup>41</sup> and the more recent Mental Health Act 2007 in the UK<sup>42</sup> which stipulate assessment of the patient’s level of “proper” understanding of a given situation. Some similar models even suggest the necessity for critical reflection,<sup>43</sup> but a deeper look at each of these models makes evident the enormous dependence of an individual’s practical possibility of exercising autonomy on the method of competence assessment used by the authority. This contrast between authority and autonomy, as well as the varied means of assessing the competence of patients suffering from different forms of mental impairment, are crucial aspects of this way of understanding autonomy.

Andrea Lavazza sensibly suggests<sup>44</sup> that autonomy *is not* an all-or-nothing concept, but in each individual, it can span from a minimum to a maximum and it is a matter of conventions to set the minimum level of autonomy to give one's consent in each situation.

Capacity can collapse into autonomy if the latter is appropriately defined and it comes in degrees. For Lavazza, autonomy amounts to a specific set of neuropsychological capabilities, which can be amenable to objective assessment and quantification.

## 2.2. The idea of capacity

A conceptualization of autonomy that tries to avoid both the stall of the metaphysical debate and the difficulties of neuroscience and empirical psychology, still partial and controversial, is linked to the idea of “capacity”. By capacity, in this context, one means the availability of a repertoire of general skills that can be manifested and used without the moment by moment conscious control. Responsible persons are those with the adequate level of mental capabilities, namely those that are necessary in order to be moral agents. A person can be held accountable for their behavior if their actions are the outcome of mechanisms that confer upon this person mental capacities such as the ability to perceive the world without illusions, to think

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<sup>41</sup> Mental Capacity Act, 2005, available at: [www.opsi.gov.uk/acts/acts2005/ukpga\\_20050009\\_en\\_1](http://www.opsi.gov.uk/acts/acts2005/ukpga_20050009_en_1)

<sup>42</sup> Mental Health Act 2007, available at: <http://www.legislation.gov.uk/ukpga/2007/12/contents>

<sup>43</sup> See, amongst others: Dworkin, G., *The Theory and Practice of Autonomy*, CUP, 1998.

<sup>44</sup> Lavazza, A. 2017. I-Consent December Workshop. *Forthcoming*

clearly, to drive their own choices in light of their judgement, and to resist the impulse of acting instinctively. The central idea is therefore that of mental abilities.

The compatibilist view of responsibility (meaning the ability to answer for one's actions, and to assume the consequences at the cognitive level and subsequently at the moral one) is well illustrated by Fischer and Ravizza.<sup>45</sup> Based on their theory, one can say that this kind of responsibility (which is the premise to moral responsibility), whether or not determinism holds true, is based on control – not regulative control, which assumes the possibility of doing otherwise, but guidance control, which “should be understood in terms of two elements: the agent's ‘ownership’ of the mechanism that actually issues in the relevant behavior, and the ‘reasons-responsiveness’ of that mechanism. So, for example, an agent is responsible for an action, on our account, to the extent that this action issues from the agent's own, reasons-responsiveness mechanism”.

Fischer and Ravizza's argument holds that in order to be responsible, some form of control is necessary – the type of control which, for example, a driver who wants to turn right and succeeds in doing so by bringing the necessary skills to bear, even though a mechanical malfunction prevents the vehicle from turning left. Assuming one has guidance control, the second condition holds that one must be able to understand the reasons behind a certain behavior and be able to apply them to one's own actions.

If, according to Fischer and Ravizza, cerebral lesions or mental illnesses can impair the guidance control, this does not happen when the agent is reasons-responsive. When an agent is (for example) hypnotized, he is not sensitive to reasons in the appropriate way. But if instead – assuming one is not under the influence of seriously pathological influences, manipulations, or situations – an agent ponders whether to turn part of her salary over to a charity organization, weighs the pros and cons, and reaches the decision to devote that sum, the agent can be considered responsible and be praised for an altruistic choice to help the poor. The difference thus lies in the ability – which can manifest itself in various degrees – to respond to reasons with a measure of guidance control. A key ingredient in the suggested account is regular reasons-receptivity. This sort of receptivity involves a coherent pattern of reasons-recognition. More specifically, it involves a pattern of actual and hypothetical recognition of reasons that is understandable by some appropriate external observer. And the pattern must be at least minimally grounded in reality. This approach based on capacity and cognitive control encompasses a synthetic idea of freedom and responsibility useful precisely for moral and legal contexts.

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<sup>45</sup> J.M. Fischer, M. Ravizza, *Responsibility and Control: A Theory of Moral Responsibility*, Cambridge University Press, Cambridge 1999.

## 2.3. Operationalizing autonomy

The ultimate goal of any project that seeks additional degrees of certainties in assessing the presence or absence of the required competence necessary for informed consent to be legitimate and credible is to overcome the interpretative and factual controversies with an operationalization and measurement of the capacities that identify the freedom-responsibility, or autonomy, of the subject. The so-called interpretative controversies would be overcome by finding a specific and operationalized definition, on the basis of reliable data that can be gradually made more precise with the refinement of the tools and the integration of theoretical knowledge. In other words, the aim is to make someone's degree of autonomy measurable, by resorting to the abovementioned notion of capacity. The so-called factual disputes concern instead the actual possession by the given individual of the abovementioned capacities and control that make her free and responsible. In other words, the aim is to establish in an increasingly precise way the extent to which a person is autonomous in terms of capacity and control.

The cognitive abilities we mentioned could be operationalized as a set of neuropsychological tests. They would be used to measure specific executive functions, central to the idea of control. Executive functions, or control functions, allow one to organize and plan one's behavior.<sup>46</sup> These skills are required to perform intentional activities, aimed at achieving objectives, monitoring and performing multiple tasks simultaneously, changing behavior based on feedback on the results obtained. They are involved in tasks of abstraction, inventiveness, judgment and criticism. A potential deficit would be evident in daily living, manifesting itself as inappropriate social behavior, problems in decision making and in the ability of critical judgment, difficulty in conceiving, performing and changing action plans adapting them to changes in the environment, excessive distractibility, and so forth.<sup>47</sup>

In general terms, the executive functions refer to the set of mental processes necessary for the development of cognitive-behavioral patterns adaptive in response to new and demanding environmental conditions.<sup>48</sup> The domain of executive functions includes:

- the ability of planning and evaluation of effective strategies in relation to a specific purpose related to the skills of problem solving and cognitive flexibility;

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<sup>46</sup> A. Baddeley, B. Wilson, *Frontal Amnesia and the Dysexecutive Syndrome*, in: "Brain and Cognition", vol. 7, n. 2, 1988, pp. 212-230.

<sup>47</sup> P.W. Burgess, T. Shallice, *The Relationship between Prospective and Retrospective Memory: Neuropsychological Evidence*, in: M.A. Conway (ed.), *Cognitive Models of Memory*, Psychology Press, Hove (UK) 1997, pp. 74-90; G.A. Gioia, P.K. Isquith, S.C. Guy, L. Kenworthy, *Test Review Behavior Rating Inventory of Executive Function*, in: "Child Neuropsychology", vol. 6, n. 3, 2000, pp. 235-238.

<sup>48</sup> P. Rabbitt (ed.), *Methodology of Frontal and Executive Functions*, Psychology Press, Hove (UK) 1997

- inhibitory control and decision-making processes that support the selection of functional response and the modification of the response (behavior) in relation to changing environmental contingencies;
- attentional control referred to the ability to inhibit interfering stimuli and to activate the relevant information;
- working memory referring to the cognitive mechanisms that can maintain online and manipulate information necessary to perform complex cognitive tasks.

## 2.4. Decision Making Capacity

Hence, an individual -like a child- who is judged to have limited autonomy, lacking therefore the required minimum level of decision making capacity (DMC) to consent, for example, to medical treatment, remains under the control of others. An interesting study by Steve Clarke<sup>49</sup> has recently attempted to engage more directly on how discoveries in neuroscience could lead us to different guidelines concerning the assessment of the competence to consent.

Clarke validly brings to our attention a number of relevant points. Firstly, he rightly stresses that competence is a threshold competence, meaning that the assessment of who is competent is a political, rather than scientific, choice. In support of this claim, he points out how the threshold to be defined by society as “fully competent” changes from country to country. Secondly, he imagines a near future in which we will be able to assess competence with a more scientific method, namely through a test able to assess with extreme accuracy the level of neuronal activity in our brain if/when exercising our competence (to consent). He goes on highlighting three issues that positions defending the *status quo* (assessing competence without the use of tests shaped by our neuronal activity) could consider as a challenge. These are cognitive privacy, a lowered threshold and the improvement of people’s competence to consent. Clarke defends that none of these arguments would suffice to justify a rejection of a - soon to be achieved- neural test of competence to consent.

Speculations over the impact of neuroscience on situations where informed consent and competence are required are not limited to that hypothetical scenario of course, but they can be a spearhead for some of the -related- key questions that need to be addressed when analyzing the ethical component behind new guidelines concerning informed consent and clinical research

## 2.5. Concrete deliverables

As the main objectives of this project are to identify gaps, barriers and challenges, and prioritize needs, requirements and areas for action in the process of informed consent; develop tailored

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<sup>49</sup> Clarke, S., “The Neuroscience of Decision Making and Our Standards for Assessing Competence to Consent”, *Neuroethics*, 6, 2013, p. 189-196.

strategies to improve and innovate the informed consent process; create and validate guidelines to design comprehensive consent forms and strategies that foster citizens' participation in clinical research and validate procedures for obtaining informed consent in vaccinations, it also important to take into consideration some concrete deliverables that should result from an analysis of the innovations that neuroscience could bring to the informed consent debate. We suggest three here.

### 2.5.1. Concerning Minors

Related to Clarke's points, neuroscience has the potential to show with more accuracy than ever when competence is reached objectively. For example, a recent study<sup>50</sup> has identified Laminin  $\alpha 5$  as the molecule capable to make the brain switch from an adolescent phase (incompetent) to an adult one (competent). Considering that within the EU there is no unanimity even in identifying a standard "age of consent" for what concerns clinical trials,<sup>51</sup> should EU policies not be more invasive in this respect (i.e. enforcing a test of neural activity in controversial cases)? Perhaps yes, if we were to guarantee more freedom of expression and action to those entitled to do so (e.g. a 13 years old girl proven through the "neurotest" to have the DMC level of an adult and not willing to follow the parents' directive concerning her medical treatment), but with great awareness of the fact that a) there is always room for a re-interpretation of what society can consider the DMC threshold and b) such an interference with the parents and family should also take into account the clash that the person-centered version of autonomy at the base of the conceptualization of DMC is not shared by all groups in society. In relation to this latter point, it is important to consider and legislate over the impact that a conceptualization of competence as a scientifically standardized achievable status would have in broader terms. Once established that competence can be reached through the achievement of certain neurobiological states and levels, temptation may abound to "enhance" such a process and speed it up through a number of already existent tools -such as Deep Brain Stimulation for instance.<sup>52</sup> When considering minors, attention should abound when legitimizing a more permissive approach towards the implementation of such technological advancements as they can represent a more structural.

### 2.5.2. Concerning Vulnerable Groups

In the light of the gender aspect taken into consideration by the project, it is important to consider the specific role that soldiers (for the vast majority, if not all, males in this case) have

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<sup>50</sup> CNS Neurons Deposit Laminin  $\alpha 5$  to Stabilize Synapses, Omar, Mitchell H. et al., *Cell Reports*, Volume 21, Issue 5, 1281 - 1292

<sup>51</sup> Informed Consent for Paediatric Clinical Trials in Europe 2015, published on 14 June 2017 Developed by the Working Group on Ethics: Pirkko Lepola, Allison Needham, Jo Mendum, Peter Sallabank, David Neubauer, Saskia de Wildt

<sup>52</sup> Maslen H, Earp BD, Cohen Kadosh R, Savulescu J. Brain stimulation for treatment and enhancement in children: an ethical analysis. *Frontiers in Human Neuroscience*. 2014;8:953. doi:10.3389/fnhum.2014.00953.

in relation to informed consent and clinical research. Since the beginning of times soldiers have been the ideal prototype for “guinea pigs” experiments, but this does not escape the fact that they are in a particularly vulnerable position. Though technically fully autonomous individuals and certainly consider having DMC, their actual level of freedom of expression and action is unique: they must follow orders, and this creates a tension currently overlooked and in need to be addressed with more attention -perhaps ensuring the defense of the newly defined right to cognitive liberty<sup>53</sup> through relative new documents and protocols to be signed off when joining the army. The idea of being able to grasp more details of how our brain functions is fascinating and worth the scientific effort, but it inevitably opens the same door as all new technologies do: that of misuse. In the case of soldiers, it appears evident that much has to be clarified in relation to their potential loss of certain cognitive rights not yet defended in the official documents of the international community but increasingly considered in the literature and requiring to be urgently implemented also in the EU as a form of regulating a still unexplored territory that risks to produce large number of newly vulnerable groups of people.

### 2.5.3. Concerning Multiculturalism and Neuroscience

Studies in neuroscience have shown that different sociocultural background can result in paying attention to different details when processing a similar situation<sup>54</sup> (i.e. being interviewed by a doctor explaining the clinical trial procedure). Hence, it would be important to investigate further how these discoveries could and should shape new guidelines concerning informed consent. In particular, it would be important also to take into account the a priori bias of the researcher in building certain -neuroscientific in this case- products. For example, a recent case in a hotel in Atlanta showed that a Black person was not recognized by the soap dispenser when passing his hand under the machine.<sup>55</sup> This also has been shown to happen for what concern face recognition.<sup>56</sup> Clearly this had to do with the engineers building the machine with certain bias (most of them being white in this case) that we cannot afford to spread in the shaping of any neurotechnology developed in the future -as this would be even more disturbing considering its more internal domain. Hence less evident and more likely to be discovered in all its ridiculousness as in the case of the soap dispenser.

## 2.6. Concluding remarks

Some important conclusions concerning the interconnection between informed consent and neurobioethics can be drawn. To begin with, it is important to stress that -given that autonomy and competence are not fixed notions untouched by interpretation- the idea of reaching full

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<sup>53</sup> Bublitz, Jan Christoph; Merkel, Reinhard (2014). "Crime Against Minds: On Mental Manipulations, Harms and a Human Right to Mental Self-Determination". *Criminal Law and Philosophy*. 8: 61.

<sup>54</sup> Culture Wires the Brain: A Cognitive Neuroscience Perspective, Denise C. Park and Chih-Mao Huang, *Perspect Psychol Sci*. 2010 July 1; 5(4): 391–400. doi:10.1177/1745691610374591.

<sup>55</sup><https://mic.com/articles/124899/the-reason-this-racist-soap-dispenser-doesn-t-work-on-black-skin#.n5lm1aloi>

<sup>56</sup> <https://www.recode.net/2017/1/18/14304964/data-facial-recognition-trouble-recognizing-black-white-faces-diversity>

agreement on who is to be defined as competent is not realistic. We might reach more accurate methods to read and categorize our brain activity, but that will not be enough to define one's competence in a schematic way. This links directly with another specific aspect of the neurobioethical concerns, namely what would be the consequences of reaching an identification of the neural correlates of the ordinary decision-making process behind the notion of informed consent? They could be helpful to categorize more convincingly the presence or absence of DMC in certain specific context (e.g. a criminal in a trial claiming to lack capacity), but they should not be seen and described as definitive proof of autonomy -especially in the light of the fact that not all cultures and approaches share the person-centered version of it that is central to the notion of informed consent. This aspect will be analyzed more in details in the next chapter, but here the pressing aspect that needs to be considered is the following: given that cultural biases have been proven to exist also at a neuronal level, in which way should we filter such an information in relation to informed consent? In other words, would it be appropriate to re-caliber certain cultures adverse attitude towards informed consent through brain re-modulation if possible? The answer is no. Not only we would crush the values of the multicultural society we live in -damaging the less represented, and hence more vulnerable, groups-, but we would also portray an inaccurate picture of the potential result as something necessarily positive in itself while aware of that not being the case. Lastly, it is clear that cognitive and other enhancers might paradoxically create new groups of vulnerable populations (e.g. soldiers), and such an awareness calls for extreme care. It is mandatory to take into account calls for new human rights, among which considering the role of cognitive liberty, mental privacy, mental integrity and psychological continuity.<sup>57</sup>

“In sum, we are not only our brains or biology, neither only our emotions or our social or cultural belongings, but a unique combination of all these dimensions. The environment and human relations, experiences, developed in specific contexts, impact our perceptions and shape our behaviors in an original manner, which cannot be explained exclusively at the level of neurobiological activity. Concerning the relationship with the patient in the informed consent process, the physician relies on highly technical scientific knowledge gained through medical education and professional training, developed over time, as well as being shaped within specific cultural and social contexts. Although, despite existing situations of shared cultural horizons between physicians and patients, therapeutic choices are likely to give rise to conflicts, since they are unavoidably influenced by many factors, which go beyond scientific-based reasons. A plurality of patterns relating to cultures, traditions and religious beliefs permeates each and every individual, and contributes to forming personal identity; this is all the more evident with migrants, where cultural diversity results in significantly different lifestyles compared to the ones conducted by the local population. In addition, also within a community of migrants sharing the same language and geographical origins, it is possible to devise considerable differences among individuals in terms of biography and cultural backgrounds, including different literacy levels (i.e. people with a low educational level,

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<sup>57</sup> Ienca, M., & Andorno, R. (2017). Towards new human rights in the age of neuroscience and neurotechnology. *Life Sciences, Society and Policy*, 13(1), 5.



alongside those with a university-level education). Therefore, it is important to overcome stereotypical thinking and standardized ways of performing medical assessments when addressing multicultural issues in informed consent (accordingly, avoiding using a “one for all” communication method): for this reason, there should be an adequate re-consideration of the importance of adopting an effective patient-centred approach (promoting an holistic approach to patient care), which reveals its urgent necessity and appropriateness, especially (although not only) with regard to a physician-patient relationship involving foreign patients or research participants; we should never overlook the fact that we are first and foremost dealing with persons, not merely with cultures, each of whom carries along a complex and unique “cultural heritage” (relating to one or more cultures), that shapes his/her “cultural identity”. Effectively facing communication barriers deriving from asymmetry in the physician-patient relationship means designing communication strategies based on a “narrative approach” to illness and suffering (i.e. modes of perceiving and conveying states of illness and pain, which can be far from the physician’s way of interpreting them, also due to his/her different cultural background): in this way, the physician attempts to foster even a “cultural relationship”, in order to decode expressive codes, not only limited to language, but equally relating to behavior. In clinical research settings, this narrative approach may help to improve the researcher-participant relationship, where participants are encouraged to share their perceptions of benefits, risks and burdens involved in a specific study or trial (also regarding particular requirements or methods used), as well as their specific understanding (from a general point of view) of what a benefit or bearable/unbearable burden or risk might be, and to what extent they can be justified. Hence, devoting attention to the cultural backgrounds of patients or research participants can contribute to achieving a more respectful, complete and effective informed consent process.”<sup>58</sup>

It appears evident then, that the interpretative dimension of autonomy, competence and consent do not only derive from our neurological state, but also from the socio-cultural context in which we make a decision. Hence, it is in line with this awareness and the very appropriate consideration by Loredena Persampieri, the next chapter will take a closer look at the relationship between informed consent and multiculturalism.

### 3. A Multicultural and Interreligious Perspective on Informed Consent<sup>59</sup>

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<sup>58</sup> Persampieri, L. 2017. I-Consent December Workshop. *Forthcoming*

<sup>59</sup> This chapter is the result of an international workshop held on February 21-23 2018 at Ateneo Pontificio Regina Apostolorum in Rome -where we gathered a number of experts in the field of multiculturalism and interreligious dialogue so to include their knowledge in the report. Experts were invited to give their insights and comments about a working document with some keys questions to be addressed. The working document was elaborated based on a narrative review of relevant and focused scientific literature. In addition, experts received reading material ahead of the workshop. The contributors were then asked to send a written paper in which they responded to some of the points, while addressing those and other issues in the discussions occurred during the workshop.

### 3.1. Autonomy, Informed Consent and Multiculturalism

In line with what discussed in the previous chapter, the UNESCO International Bioethics Committee stressed in more than one occasion that an individual has to be informed as much as possible on the outcomes of the procedure in which she is involved in: “The close connection between autonomy and responsibility supposes that consent be freely given by the person concerned, the clearest possible information be provided, his/her faculties of comprehension be intact, that he/she has been able to assess the consequences of participating in a research project and the development of the entire process, as well as fully understanding the advantages and disadvantages of possible alternatives, also in terms of treatment.”<sup>60</sup>

Aside from this analysis, various cultural and social variables are to be taken into account when assessing the ethical validity of the informed consent process. Often, such considerations might impinge upon the monolithic, person-centered version of autonomy that we tend to give for granted in the Western contexts, creating a space for new versions of vulnerability -in which the vulnerable population is represented by those individual unable to see their attitude and perception of autonomy as sufficiently represented by current legislations. In some scenarios for example, “communal autonomy” o “relational autonomy”, a version of autonomy that sees the deliberation and the legitimacy of a decision to belong not only to a single person, but rather the community to which one belongs (i.e. family). Often leaders of the community - nearly always family members- are those who make the decisions and their judgment is not questioned due to their age, expected wisdom and knowledge of the community’s internal dynamics in place.

### 3.2. Individual and Relational Autonomy

In line with what just described, the words of Joseph Tham and Marie Letendre are particularly relevant to understand more accurately how some of our standard ways of conceptualizing the discussion around informed consent might not be as given as expected.

“Cultural norms specify behavior. ‘Honesty is an ideal value for most Americans, but it varies in strength as a real value for other cultures.’<sup>61</sup> Honor is highly prized in the Japanese culture as is female purity in the Islamic world. Direct eye contact is avoided in several cultures, notably Asian and the Middle Eastern culture; the Navaho use silence to formulate their thoughts in order to give the most complete answer. Trust is given only to family members in the Gypsy culture. Masculine and feminine pronouns do not exist in Asian languages, and ‘yes’ does not always mean the affirmative since many cultures use the ‘yes’ as a way of avoiding an embarrassing ‘no’. This is just a short list of cultural variables that inform and form communication styles. A cross-cultural health care ethic combines the tenets of patient- family centered care with an understanding of the social and cultural influences that affect the quality

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<sup>60</sup> UNESCO IBC 2008, 15

<sup>61</sup> Spector, R. 2000. *Cultural Diversity in Health and Illness*. Prentice Hall, Upper Saddle River, New Jersey. Surbone, A. 2006. Telling the truth to patients with cancer: what is the truth? *Oncology*, 7, pp.994–950.

of medical services and treatment. Developing sensitivity to different cultures can make health care programs and activities attractive and interesting for a broader population base. In contrast, a lack of cultural sensitivity can deter people from using health care services.”<sup>62</sup>

Hence, not all documents that assume that focusing on the individual might be sufficiently sensitive towards how one person with a cultural, religious or identitarian background might want (or is capable) to express her views, values and desires if disconnected from her community. In accepting this reality, it is equally important to bear in mind, as Loredana Persampieri rightly stresses, that -though contemplated- relational autonomy has no effective role in the shaping of informed consent in official forms.

“Seeking consent from an individual is necessary, even if the community is consulted, but the actual value of the consent of such individual, once the community has given its approval or disapproval, often raises concern. Nevertheless, such reasons should not lead to the conclusion that cultural considerations pave the way to situations where, exceptionally, for members of some groups communal autonomy may override individual autonomy. Conversely, we should always bear in mind that “respect for cultural diversity and pluralism should not be used to infringe fundamental freedoms nor any of the principles set out in the Declaration”.<sup>63</sup> In this perspective, the Italian National Bioethics Committee suggests an interpretation of the concept of autonomy in terms of “relational autonomy”, which may be better tailored to an intercultural approach aimed at accommodating the value of the community dimension in certain cultural settings (i.e. African tribes) and respect for the person<sup>64</sup>.”<sup>65</sup>

As the notion of informed consent relies on a set value of individual autonomy that not all cultures and approaches to life share, a patient’s cultural disposition and past experiences with medical health care professionals will have an impact on the amount of trust that they can have in a vaccines’ efficacy for example. Although local culture may shape people’s perception over time, people are more likely to trust experts that share a similar background, tradition, religion and culture with them.<sup>66</sup> When working with ethnic minority patients, it is important to note that comprehension may also transcend simply linguistic barriers. The conceptualization of illness and cultural bias both play a role in the ways that information is presented and understood. Thus, it is important to understand the role that culture plays in obtaining informed consent.<sup>67</sup> In particular, in multicultural societies, where a large portion of the society is made up of immigrants with varying cultural backgrounds, there may be differing attitudes regarding the role of physicians. Moreover, the quality of informed consent may be dependent

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<sup>62</sup> Tham, JS, Letendre, MC, Health Care Decision Making: Cross-Cultural Analysis of the Shift from the Autonomous to the Relational Self, *The New Bioethics*, Vol. 20 No. 2, 2014, 180-181

<sup>63</sup> Art. 12, UNESCO Declaration on Bioethics and Human Rights, 2005

<sup>64</sup> NBC 2017, 38

<sup>65</sup> Persampieri, L. 2017. I-Consent December Workshop. *Forthcoming*

<sup>66</sup> Kahan DM, Braman D, Cohen GL, Gastil J, Slovic P. Who fears the HPV vaccine, who doesn’t, and why? An experimental study of the mechanisms of cultural cognition. *Law and human behavior*. 2010 Dec 1;34(6):501-16.

<sup>67</sup> Dein S, Bhui K. Issues concerning informed consent for medical research among non-westernized ethnic minority patients in the UK. *Journal of the Royal Society of Medicine*. 2005 Aug 1;98(8):354-6.

on the relationship between a physician and their patient. To improve the physician-patient relationship, and for the consent gained to be effective, there has to be a partnership based on openness, trust, and good communication between the two parties. Individual's religious beliefs or related cultural values can lead to questions and concerns that health professionals, unfamiliar with the religion or culture, have not encountered before. Not only does an immigrant have to trust the medical personnel, but also the attitude that the vaccinators display towards the immigrant has to be positive. It has been shown that culture, (which can also include religious and spiritual backgrounds), can impact one's vulnerability to infectious diseases. Rejecting vaccination due to religious or cultural values is not a new phenomenon; there have been reports of vaccines-preventable outbreaks in religious schools, congregations and religious communities. As a case study, the World Health Organization reported that in a region in Nigeria 16% of the children were vaccinated against polio. The reason for the low vaccination rates is that the community is predominantly Muslim, and they believe that the polio drops are used as a tool to sterilize the children. Likewise, a study from the Netherlands has shown that municipalities with high orthodox protestant domination have lower vaccination rates compared to municipalities without an orthodox protestant domination.

A discussion of the views that every religion or culture has with regards to the link between informed consent and clinical research vaccination programs is outside the scope of this project. Still, here the focus will concern six of the major religious and cultural traditions (Buddhism, Christianity, Confucianism, Hinduism, Islam and Judaism) with respect to immunization (i.e. vaccination programs). These specific religions and cultures have been selected due to their prominence in the Western context (above all, Europe), as well as the fact that, together, they represent an extremely high percentage of the world's population.

Buddhism	<ul style="list-style-type: none"> <li>● Major Buddhist sects include Theravada, Mahayana, Vajrayana, and Zen. Buddhism has no central authority empowered to pronounce on doctrine or ethics.</li> <li>● Vaccination is widely accepted in predominantly Buddhist countries.</li> <li>● Buddhism does not oppose treatment of an existing illness by use of non-animal derived medicines, because treatment is an act of mercy.<sup>68</sup></li> <li>● The first written account of variolation describes a Buddhist nun (<i>bhikkhuni</i>) practicing around 1022–1063 CE.<sup>69</sup> She ground scabs taken from a person infected with smallpox (variola) into a powder, and then blew it into the nostrils of a non-immune person to induce immunity.</li> </ul>
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<sup>68</sup> Ratanakul P. Buddhism, health and disease. Eubios J Asian Int'l Bioeth 2004;15:162–4. Available from: <http://www.eubios.info/EJ145/ej145b.htm>

<sup>69</sup> Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. Smallpox and its eradication. Geneva World Health Organization; 1988.

	<ul style="list-style-type: none"> <li>Continuing this tradition, the 14<sup>th</sup> Dalai Lama participated in poliovirus immunization programs personally.<sup>70</sup></li> </ul>
Christianity	<ul style="list-style-type: none"> <li>There are various Christian denominations, and most of the denominations have no objections to the use of vaccinations.<sup>71</sup></li> <li>According to Grabenstein, the denominations with no objection include Roman Catholicism, Eastern Orthodox and Oriental Orthodox Churches, Amish, Anglican, Baptist, the Church of Jesus Christ of Latter-day Saints (LDS), Congregational, Episcopalian, Lutheran, Methodist (including African Methodist Episcopal), Pentecostal, Presbyterian, and Seventh-Day Adventist Church.</li> <li>Jehovah's Witnesses' authorities have taken a neutral position on vaccination, and they have stated that blood derivatives may be accepted on certain occasions.</li> <li>The Roman Catholicism and a few other Christian denominations have expressed some concern with respect to the "aborted fetal origins of the principal formulation of rubella vaccine and some cell lines used to manufacture certain types of viral vaccines".</li> </ul>
Confucianism	<ul style="list-style-type: none"> <li>Confucianism has been the considered the guiding line in traditional Chinese Medicine for millennia.<sup>72</sup></li> <li>It appears that there is no specific guideline concerning immunization, but duties are as important as rights in Confucianism.</li> </ul>
Hinduism	<ul style="list-style-type: none"> <li>Vaccination is widely accepted in predominantly Hindu countries.</li> <li>The Hindu and Buddhist religions have long prioritized respecting all forms of life, in the form of ahimsa. Differently from the Jains -who extends this respect even to the bacteria or viruses contained in a vaccine- Hindus allow for some elasticity in this interpretation. As, Mohandas Gandhi observed: "The very fact of his [humanity's] living—eating, drinking and moving about—necessarily involves some <i>himsa</i>, destruction of life, be it ever so minute."<sup>73</sup></li> </ul>

<sup>70</sup> Monthly Situation Reports, Dec 2009 and Jan 2010: endemic Countries, India. Geneva: Global Polio Eradication Initiative; 2010. Available from: <http://www.polioeradication.org/Mediaroom/Monthlysituationreports/2010/January.aspx>

<sup>71</sup> Grabenstein JD. What the world's religions teach, applied to vaccines and immune globulins. *Vaccine*. 2013 Apr 12;31(16):2011-23

<sup>72</sup> Jingfeng, Cai (1998). A historical overview of traditional Chinese medicine and ancient Chinese medical ethics. *Ethik in der Medizin* 10 (1):84-91.

<sup>73</sup> Gandhi MK. An autobiography: the story of my experiments with truth (1920). Mineola, NY: Dover Publications; 1983.

	<ul style="list-style-type: none"> <li>● Verses of the Rig-Veda refer to the cow as <i>devi</i> (goddess), but Hindus do not worship cows, but rather venerate (deeply respect) them. To our knowledge, contemporary Hindu authorities do not show concern with trace bovine components of some vaccines.</li> </ul>
Islam	<ul style="list-style-type: none"> <li>● Many Islamic leaders have issued statements to inform their followers that immunization is in line with the Islamic principles.</li> <li>● There is also the importance of protecting others through the vaccines and the rule to protect all lives.</li> <li>● The dietary concerns can be eliminated for the sake of advancing the medical health of an individual.</li> </ul>
Judaism	<ul style="list-style-type: none"> <li>● Judaism allows the believers to take certain proactive measures to maintain one's health</li> <li>● Judaism places a high regard for community health, and there is a duty to protect one's children and neighbors from harm</li> <li>● There are some dietary restrictions on medication; in particular, the kosher limitations may apply to oral administration of some drugs, but not to injections. Even if there are dietary restrictions, the authorities still consider the importance of preserving life.</li> </ul>

Table 1: Religious views concerning vaccination. The key facts presented above illustrate the impact that religious and cultural beliefs can have on the health of a community. In his report, Grabenstein mentions the importance of collaboration between the public-health leaders and the religious leaders in order to resolve any objections to vaccination programs.<sup>74</sup>

Broadening the discussion back to the way informed consent notion interacts with biomedical research, some of the key questions that we want to address here are:

- How much of the notion of informed consent is applied in one's tradition? And in which way?
- Can or should we have different informed consent forms for differently vulnerable populations?

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<sup>74</sup> Grabenstein JD. What the world's religions teach, applied to vaccines and immune globulins. *Vaccine*. 2013 Apr 12;31(16):2011-23

- Do all traditions agree with the general principles behind informed consent (i.e. the prioritization of individual autonomy)? If not, what alternative values/approach could support widespread vaccination for example?

In the following sections different answers to these and other questions from the different traditions considered will be highlighted.

### 3.3. Considerations from Buddhism

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 “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. In addition, Buddhism would also speak of the importance of duty along with the right-talk. For example, in the case of vaccination, Buddhism will use duty rather than right to argue for it. In other words, it is not someone’s right (i.e., individual’s autonomy) to have, or not have vaccination; instead, it is someone’s duty to protect oneself and others in society through a proper prevention of the infection and its respective immunization. Since vaccination concerns public health, Buddhists today will generally use vaccines to make sure their health is protected. [...] Given that Buddhism is not a religion confined to dogmas and that it is a religion emphasizing consequentialist considerations, Buddhism would be more acceptable to vaccination that clearly concerns public health. One example to support this argument is vegetarianism. Despite that Buddhists practice vegetarianism in general, they are allowed to eat meat when there is no alternative choice.”<sup>75</sup> As shown already in the next section of the chapter, a general attitude -from individuals and from the State- that will give priority to public health and duties towards the community might not be ideal and it might also restrict our individual autonomy, but it is an approach that is shared both by other traditions and the Western secular approach.

### 3.4. Considerations from Christianity

As highlighted by Laura Palazzani, in the Christian perspective in bioethics: “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. Research should be conducted according to accepted scientific principles and it must always be deemed necessary and potentially useful for the patient. It must never subject an individual to unnecessary or disproportionate risks, which overshadow the expected benefit from the research. The researcher must never participate in projects that may involve the treatment of

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<sup>75</sup> Zhang, E. 2018. I-Consent February Workshop. *Forthcoming*

the human subject as an object of that interest. Studies which may involve immoral cooperation with evil must be avoided.”<sup>76</sup>

More specifically in relation to Roman Catholicism, although once more controversial in their use, vaccinations are nowadays accepted as morally sound and exemption is not required anymore.<sup>77</sup> In fact, the Vatican has produced a large number of documents and statements<sup>78</sup> in which support of widespread vaccination, establishing in clear terms that the balance between risks and benefits for both the individual (the primary concern of biomedical research) and the community is not put at risk by the practice.

### 3.5. Considerations from Confucianism

In the Confucian tradition, the link between the medical and political sphere is even more evident and Ruiping Fan expresses some of the peculiarity of this way of seeing the world and processing what the best way of behaving between and towards society is. Medicine is subordinated to politics as a way of benefiting society, hence the last call for any medical decision that concerns public health is given to politics. “Confucianism sees medicine as “the art of *ren*” (*renshu*), in contrast of seeing politics as “the governance of *ren*” (*renzheng*). This indicates that both medicine and politics are taken to be the virtuous causes of humanity, but politics is more important than medicine perhaps because it can benefit people more than medicine in the proper context. Indeed, in the tradition medicine has been termed “the little *dao*” (*xiaodao*), while politics “the great *dao*” (*dadao*).<sup>79</sup> Meanwhile, both traditional Confucian politics and medicine have a meritocratic and paternalistic tendency: only virtuous persons should become politicians or physicians, and they should make decisions to promote people’s welfare in light of their own professional knowledge and judgements. On medicine, Confucian physician ethics has been similar to the Hippocratic Oath ethics in terms of medical professional obligations. It is the health and well-being of people that constitute the end of the art of medicine, but the judgment of such health and well-being lies in the hands of the physician. Throughout the history of Chinese medicine, the emphasis has always been placed on the

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<sup>76</sup> Palazzani, L. 2018. I-Consent February Workshop. *Forthcoming*

<sup>77</sup> There is a discussion on the position of Pope Leo XII (1823-29) who is reported as against vaccination: “whoever allows himself to be vaccinated ceases to be a child of God. Smallpox is a judgement of God, the vaccination is a challenge toward heaven” (reported in K. McGovern, K.A. Brussen, *Ethically compromised vaccines and Catholic teaching*, “The Nathaniel Report”. April 2012, 36, p. 13.

<sup>78</sup> Pontifical Academy for Life. <http://www.academyforlife.va/content/pav/it/the-academy/activity-academy/note-vaccini.html>

<sup>79</sup> As a Confucian politician, Fan Zhongyan (989-1052), has famously stated: “if one cannot become a good premier, one should become a good physician.” His reason is as follows: “If one can become a good premier and implement the *dao* of a sage king, one will be able to benefit everyone under-the-Heaven, both nobles and ordinary men. However, if one is not able to become a good premier, then nothing is better than becoming a good physician to practice the art of saving humans and benefiting things. Only a good physician, although staying below, is able to offer help to both his superiors and subordinates. To his superiors he can cure the ailments of his parents and emperor, to his subordinates he can rescue them from their maladies, and to himself he can preserve his life and pursue longevity”. Fan, R. “The Discourses of Confucian Medical Ethics,” in the *Cambridge World History of Medical Ethics*, ed. Robert Baker and Laurence McCullough, CUP, Cambridge, 2009, pp. 195-201.



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." Fan continues in explaining that: "Contemporary Confucianism must explicitly reject physician paternalism because it violates a right to informed consent that Confucianism should accept. As discussed in the first section, individual rights, as a moral and legal mechanism, are necessary to protect legitimate individual interests which are essential for a comprehensive good human life, even if they are not essential for a virtuous human life. For the sake of patients' legitimate interests, physicians must be required to provide relevant medical information to patients and their families. It should be patients and their families, rather than physicians, that have final authority to decide about medical care issues for themselves."<sup>80</sup> The settle aspect that must be taken into account is the balance between the inclusion of the family and the preservation of individual autonomy as the final, decisive notion of reference when deciding what to do with the patient or subject. There is room to for a more sensitive attitude towards familiar networks and that is another linking ring with other traditions -not last the next one considered.

### 3.6. Considerations from Hinduism

Hinduism is the main representative of the Indian subcontinent cultural background -though certainly India's multiculturalism relies on other important traditions such as Buddhism, Christianity, Islam and Sikhism- and, with this knowledge in mind, John Lunstroth tells us: "the peoples of the subcontinent all share a concern for life and genuine friendliness and compassion for the other. This is their *dharma*, a central feature of their way of life. But it would be a mistake to think of *dharma* as meaning just that. *Dharma* also means law/right, in its broadest sense, and through this set of meanings it reads for government. *Dharma* is the organizing principle of each of the different stages of life, but it has particular salience for the householder because of its linkage to government and to the principle of doing the right thing, and because it is associated as a structural principle with *artha* and *kama*, the two driving forces of householder life. Sannyasins (and those retreating from life) are in significant ways of no concern in this calculus<sup>81</sup>."<sup>82</sup> In other words, India represents a context in which people feel at the same time a duty and to act in accordance to the law -that prescribes them to care about the others- but this very "imposition" overlaps with a genuine, altruistic tendency to want to benefit and help the other. The bi-dimensional use *dharma* in this sense, shows the richness that can be derived (also by other traditions and secularists) from the consideration of other

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<sup>80</sup> Fan, R. 2018. I-Consent February Workshop. *Forthcoming*

<sup>81</sup> Swami Rama relates a remarkable story of how, when he was a young renunciate, he was walking in a mountain wilderness when he slipped and was severely injured. Pilgrims and others would simply walk by him as he suffered, secure in the knowledge that as a spiritually advanced being he would be fine. Swami Rama, *LIVING WITH THE HIMALAYAN MASTERS* (Himalayan International Institute, 1980).

<sup>82</sup> Lunstroth, J. 2018. I-Consent February Workshop. *Forthcoming*

points of view on matter of informed consent. This is also evident in the next tradition considered.

### 3.7. Considerations from Islam

In an approach that might be defined as a way of decolonizing the debate also in respect to terminology, Aasim Padela tells us that: “as medicine has globalized so has bioethics. 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.”<sup>83</sup> It should come as no surprise then that four-principle Georgetown model of medical ethics is widely-taught in Muslim lands, and that research and medical practice guidelines in these countries are borrowed from American and European institutions. While there has been increased attention given to formulating medical ethics guidelines based on indigenous Muslim cultural values or based on Islamic law, these efforts are in their infancy and not as yet widespread.<sup>84</sup> 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 processes and thereby necessitate a re-imagining of these procedures to suit Muslim sensibilities and culture.”<sup>85</sup> These considerations are particularly valuable for what concerns that practical side of our project, namely the awareness that further understanding of the complexities behind different cultures could help us a) deal more effectively with certain prejudice of minorities by referring to concepts more internal to the “alternative” path from that we might consider as explicative; b) implement new terminologies that could encompass slightly different approaches that could be enriching also to other communities not necessarily following that very religion or tradition and yet would benefit from an enlarged spectrum of possibilities in front of them to confront and interact with reality.

### 3.8. Considerations from Judaism

David Heyd writes: “How do all these developments in religious discussion of clinical trials, vaccinations and informed consent affect the actual way in which the orthodox religious sectors behave regarding those practices? [...] As a matter of fact, there is a lower rate of immunization in the ultra-orthodox sector of Israeli society, but the cause for that phenomenon is not easy to detect. Indeed, there were a few cases in which leading rabbis instructed their communities to avoid immunization, but this occurred on the occasion of some medical controversy about the effectiveness of particular immunization (which led also some non-religious sectors to refuse to immunize their children). There is some general suspicion on part of these

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<sup>83</sup> De Vries, R. and L. Rott, *Bioethics as Missionary Work: The Export of Western Ethics to Developing Countries*, in *Bioethics around the Globe*, C. Myser, Editor. 2011, Oxford University Press: New York. p. 3-18.

<sup>84</sup> Suleman, M., *Biomedical Research Ethics in the Islamic Context: Reflections on and Challenges for Islamic Bioethics*. Islamic Bioethics: Current Issues And Challenges, 2017. 2: p. 197.

<sup>85</sup> Padela, A. 2018. I-Consent February Workshop. *Forthcoming*

communities in the instructions of the State [of Israel]<sup>86</sup> and the Ministry of Health, but this suspicion is not derived from any formal religious argument against the idea of immunization as such. Living in small and relatively isolated communities, this sector in the population may feel that the “herd effect” of most people getting immunized is sufficient to protect them from the disease without them taking the inoculation. Furthermore, some immunizations are thought of as conveying a negative moral message, such as the inoculation against papillomavirus, which prevents cervical cancer in young women. But beyond these sociologically relevant explanations I should emphasize that the leading religious authorities do not oppose immunization and many of them strongly encourage their followers to take them, including children and some of them consider them and clinical trials even as “a holy war” against the threat of fatal illness, a war which calls for a universal draft.”<sup>87</sup> Here, a number of interesting considerations are to be made. First, the fact that there might be connection between the proximity of risk and the rate of acceptance towards a certain treatment underlines how this way of processing information does represent a problem when we think of the globe. It is additionally difficult to sensitize Westerners towards malaria if this is not present in north America and Europe. Second, the role of religious leaders can help but is not guarantee of success. Third, the “spiritual damage” (i.e. the increase risk of pre-marital sex) of a practice might be considered more important than the actual medical damage in some instances.

### 3.9. Recommendations

As the main objective of this project is to identify the ethical gaps, barriers and challenges currently present in obtaining informed consent from patients in different, challenging contexts and address the issues with some practical suggestions for future policies, two main deliverables can be extracted from the inputs here analyzed. They should be further expanded and taken into consideration when developing new models and forms that aim at providing convincing guidelines for the informed consent process.

The first aspect to take into account is the role of religious keywords. Implementation of some key terms directly referring to some religious traditions. For example, *kosher* or *halal* in vaccines, or reference to *xiaodao* and *dadao* as notions helpful to conceptualize better why we, as single individuals, should behave in a certain way in relation to society. Not only ensuring the “religious approval” from different traditions will increase the trust towards doctors and researchers, but it will also make more evident and immediate in the eyes of the believer terms that will help him filling up required forms and documents with more conviction, speeding up the process of sharing scientific information.

The second point is that international accepted notions and values such as human duties,<sup>88</sup> should be considered when discussing informed consent, not only human rights. Where

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<sup>86</sup> Added for a clarification of context by the editors.

<sup>87</sup> Heyd, D. 2018. I-Consent February Workshop. *Forthcoming*

<sup>88</sup> <http://unesdoc.unesco.org/Ulis/cgi-bin/ulis.pl?catno=188520&gp=&lin=1&ll=f>

possible, use the specific tradition to reinforce the duties towards society as a whole. For example, the principle of the public interest (*maslahat al-ummah*) that sees vaccines as a way to protect *others* in Islam. Or the idea of *dharma* in the Hindu tradition in relation to laws and duties towards society (stressed by many other traditions through different concepts, notions and approaches, but still very similar in practice).

## 4. Bias and Informed Consent

### 4.1. 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.<sup>89</sup>

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.<sup>90 91</sup>

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 less relevance with this issue.<sup>92 93</sup>

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,

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<sup>89</sup> 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.

<sup>90</sup> 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.

<sup>91</sup> Hardicre J. Valid informed consent in research: An introduction. *British Journal of Nursing*. 2014;23(11):564-7.

<sup>92</sup> 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.

<sup>93</sup> Steinberg A. Disclosure of information and informed consent: ethical and practical considerations. *Journal of child neurology*. 2009;24(12):1568-71.

appropriate, precise and relevant information should be provided in a language and format that patients fully understand.<sup>94 95 96</sup>

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 making a decision of participating in a clinical trial.<sup>97 98</sup> 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.<sup>99</sup> In the following section, it will be explored more in detail the role that investigators can have (with their bias) in the obtainment of informed consent.

## 4.2. Investigator bias in the informed consent obtaining process

What is bias? A patient should receive a different care attention because its race, gender or any other factor. However, there are existing bias, among health care professionals that contribute to health disparities.<sup>100 101</sup> Bias refers by psychologists as “the negative evaluation of one group and its members relative to another”.<sup>102</sup>

A stereotype is “a cognitive structure that contains the perceiver’s knowledge beliefs, and expectations about a human group”.<sup>103</sup> 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

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<sup>94</sup> 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.

<sup>95</sup> 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.

<sup>96</sup> 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.

<sup>97</sup> 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.

<sup>98</sup> McCabe MS, editor *The ethical foundation of informed consent in clinical research*. Seminars in oncology nursing; 1999: Elsevier.

<sup>99</sup> 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.

<sup>100</sup> 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.

<sup>101</sup> FitzGerald C, Hurst S. Implicit bias in healthcare professionals: a systematic review. *BMC medical ethics*. 2017;18(1):19.

<sup>102</sup> 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.

<sup>103</sup> Hamilton DL, Trolie TK. *Stereotypes and stereotyping: An overview of the cognitive approach*. 1986.

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 multi-cultural diversity and has no conscious negative attempts to use their stereotypes.<sup>104</sup>

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 race and ethnic beliefs have decreased significantly, being nowadays unacceptable within general society. 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's difficult to control. Implicit bias is normally associated with spontaneous non-verbal behavior such as repeatedly eye contact, sitting away from a person that's not your same race, facial expression, etc. For instance, a person could think that he or she is not racist but then, has unintentionally attitudes towards race 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 other race patients, even when they fully intend to give equal care to everybody.<sup>105 106 107 108 109</sup>

### 4.3. Recruitment of minorities

Recruitment in research is influenced by several factors that need to be identified in order to improve this process.<sup>110</sup>

When talking about minorities, recruitment for clinical trials have even more barriers and gaps that need to be addressed.<sup>111</sup> Clinical investigators have found it difficult to enroll patients from minorities due to a mistrust relationship, language differences, cultural values and limited

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<sup>104</sup> 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

<sup>105</sup> 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.

<sup>106</sup> FitzGerald C, Hurst S. Implicit bias in healthcare professionals: a systematic review. BMC medical ethics. 2017;18(1):19.

<sup>107</sup> 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.

<sup>108</sup> 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.

<sup>109</sup> Van Ryn M, Saha S. Exploring unconscious bias in disparities research and medical education. Jama. 2011;306(9):995-6.

<sup>110</sup> 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.

<sup>111</sup> 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.

access to these populations.<sup>112</sup> 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.<sup>113</sup>

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.<sup>114</sup>

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 multi-culturalism 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 multi-culturalism 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

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<sup>112</sup> 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.

<sup>113</sup> 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.

<sup>114</sup> 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.



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”.<sup>115</sup> 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.<sup>116</sup>

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.<sup>117</sup>

#### 4.4. Researcher influence

Patient decision making process could also be influenced conscious 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.<sup>118</sup> 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

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<sup>115</sup> 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.

<sup>116</sup> 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.

<sup>117</sup> 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.

<sup>118</sup> Walsh E, Sheridan A. Factors affecting patient participation in clinical trials in Ireland: A narrative review. *Contemporary Clinical Trials Communications.* 2016;3:23-31.



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.<sup>119</sup>

#### 4.5. 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.<sup>120</sup>

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?<sup>121</sup>

Regarding who should disclose the information, the doctor that best knows the patient should.<sup>122</sup>

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.<sup>123</sup>

What? The relevant and adequate information in each case should be disclosed, whatever is the best for the patient.<sup>124</sup>

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<sup>119</sup> 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.

<sup>120</sup> Williamson T. Research, informed consent, and the limits of disclosure. *Bioethics*. 2001;15(4):341-63.

<sup>121</sup> Steinberg A. Disclosure of information and informed consent: ethical and practical considerations. *Journal of child neurology*. 2009;24(12):1568-71.

<sup>122</sup> Steinberg A. Disclosure of information and informed consent: ethical and practical considerations. *Journal of child neurology*. 2009;24(12):1568-71.

<sup>123</sup> Steinberg A. Disclosure of information and informed consent: ethical and practical considerations. *Journal of child neurology*. 2009;24(12):1568-71.

<sup>124</sup> Steinberg A. Disclosure of information and informed consent: ethical and practical considerations. *Journal of child neurology*. 2009;24(12):1568-71.

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.<sup>125</sup>

#### 4.6. Ethnic/racial implicit bias: neuroscientific approach

We have seen in previous chapters 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.<sup>126</sup>

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's easy to have situations under stress, time pressure and working memory, that can lead to a cognitive overload, and thus, to a biased behavior.<sup>127 128</sup>

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.<sup>129</sup>

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

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<sup>125</sup> Steinberg A. Disclosure of information and informed consent: ethical and practical considerations. *Journal of child neurology*. 2009;24(12):1568-71.

<sup>126</sup> 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.

<sup>127</sup> 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.

<sup>128</sup> Van Ryn M, Saha S. Exploring unconscious bias in disparities research and medical education. *Jama*. 2011;306(9):995-6.

<sup>129</sup> 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.

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.<sup>130</sup>

Results have shown that the majority of implicit race 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.<sup>131</sup>

#### 4.7. Future steps: Interventions to reduce the effects of implicit bias

Implicit bias can be considered as an automatic association between two terms (implicit and bias), cue-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.<sup>132 133</sup>

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.<sup>134</sup>

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 race or 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

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<sup>130</sup> FitzGerald C, Hurst S. Implicit bias in healthcare professionals: a systematic review. BMC medical ethics. 2017;18(1):19.

<sup>131</sup> 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.

<sup>132</sup> 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.

<sup>133</sup> John-Henderson NA. Implicit Cognition. Child and Adolescent Psychiatric Clinics. 2015;24(4):751-63.

<sup>134</sup> 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.

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.<sup>135</sup>

There is also evidence that increasing the diversity of health care professionals help to reduce racial and ethnic biases.<sup>136</sup>

## 5. Improving the understanding and readability of informed consent

Sometimes, physicians and investigators fail to identify the situations where patient's capacity to consent is being altered or decreased. Patient's understanding and capacity for decision making process sometimes can be overwhelmed, especially when the information is complex, causing a very difficult consent process. Emotionally overwhelmed patients need support, while informationally overwhelmed patients need other ways of decision making. In these situations, researchers and clinicians should always discharge their obligations but more specifically focus on avoid patients becoming overwhelmed. Informed consent depends on capacity and there are three variables influencing capacity: patient-related factors, information-related factors and communication-related factors. Regarding this last one, communicating skills by the investigator is crucial for the understanding of the patient and has shown to be influential on the decision-making process. For this reason, it is important that investigators are able to reduce the effects of emotional overload through gaining expertise in communicating information and thus, facilitate understanding of the patients.<sup>137</sup>

Understanding refers to the patient's comprehension of the information disclosed in an informed consent process. Various systematic reviews that studied different interventions to improve the understanding of research consent, showed that enhanced consent forms, extended discussion and multimedia interventions, increased participant knowledge. Enhanced consent forms translate into simplified paper documents with better design, text styling, added pictures, summary sections, booklets or leaflets, page layout, revised language, shorter sentences, readability improved, less technical words, bullets, different fonts, etc. Extended discussion means to have group discussions with research staff or study nurse, additional phone conversation with researcher or nurses, supplementary conversation with the research team, detailed repetition of the information, extra meetings with educators and enrolling researcher, and so on. Multimedia interventions consist on replacing consent forms with videos, computer presentations, PowerPoint slides with audio narration, and so on. These three types of interventions have shown to improve the understanding and knowledge of the patient, especially when a study team member spend more time in a one-to-one interaction (extended

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<sup>135</sup> 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.

<sup>136</sup> John-Henderson NA. Implicit Cognition. Child and Adolescent Psychiatric Clinics. 2015;24(4):751-63.

<sup>137</sup> 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.

discussion) which seems to be the most effective intervention. However, consistency of results it's still unclear and more research is needed.<sup>138 139 140</sup>

Another study reviewed that simplified consent forms were better understood by all patients, in a comparison with standard consent forms, regardless their health literacy level.<sup>141</sup>

Regarding length of the consent forms, there is an existing problem between patient understanding and page count, as these two terms are inversely proportional, meaning that a patient understanding decreases with a higher length of the consent form. However, important information may still be missing although the consent form is long. In this way, improvements should focus on revising the content and presentation of consent forms and assure only the relevant information is present with an easy-to-read format.<sup>142</sup>

Another systematic review concluded that in general, participants understand main components of the consent form such as the nature of the study, the right to withdraw at any time, the voluntary participation, and so on. However, more specific and technical terms such as placebo or randomization were not comprehended by the patients. This suggests that investigators could apply a greater effort to help participants understand all components of the informed consent in order to ensure their correct decision-making and protect their interests.<sup>143</sup>

## 5.1. Informed Consent for Vaccination prior to the administration of vaccines

Informed consent for vaccination demands the same requirements for consent from participants as other medical interventions. To respect patient autonomy, medical professionals are first required to provide patients with adequate information. It requires clinicians and researchers, at the minimum, to provide: "information to subjects about purpose of the research, its procedures, potential risks, benefits, and alternatives (no matter how remote), so that the individual understands this information and can make a voluntary decision whether to [...] participate".<sup>144</sup> Secondly, the patients have to fully understand the information

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<sup>138</sup> Nishimura A, Carey J, Erwin PJ, Tilburt JC, Murad MH, McCormick JB. Improving understanding in the research informed consent process: a systematic review of 54 interventions tested in randomized control trials. BMC medical ethics. 2013;14(1):28.

<sup>139</sup> Flory J, Emanuel E. Interventions to improve research participants' understanding in informed consent for research: a systematic review. Jama. 2004;292(13):1593-601.

<sup>140</sup> Tamariz L, Palacio A, Robert M, Marcus EN. Improving the informed consent process for research subjects with low literacy: a systematic review. Journal of general internal medicine. 2013;28(1):121-6.

<sup>141</sup> 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.

<sup>142</sup> Beardsley E, Jefford M, Mileschkin L. Longer consent forms for clinical trials compromise patient understanding: so why are they lengthening? Journal of Clinical Oncology. 2007;25(9):e13-e4.

<sup>143</sup> 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.

<sup>144</sup> Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical?. Jama. 2000 May 24;283(20):2701-11.

provided to them, because central to the concept of informed consent is “disclosure of sufficient information in a way that is understandable to the patient.” Thirdly, patients have to voluntarily make a decision to accept or reject the treatment offered. When this process is followed, the physician is not exercising undue influence<sup>145</sup> and the patient is making an informed individualistic decision.

However, unlike other medical interventions, consent to vaccines is not entirely an individualistic decision. This is because unvaccinated individuals can present an element of risk to other members of society. Furthermore, individuals may be discouraged from obtaining vaccination since there is the incentive to “free-ride”. A “free-rider” is someone who avoids getting vaccinated but is able to benefit from another individual’s vaccination.<sup>146</sup> In such instances, the public’s vaccination status will impact an individual’s risk of infection. In one study the researchers used a computerized experimental game in order to simulate a hypothetical disease. The results of the study indicated that each participant’s vaccination decision depended on the vaccination decisions of the other participants. Throughout the study it was revealed that the free-riding behavior was present regardless of whether the hypothetical disease was “severe or mild; the risk of infection was high or low; the cost of vaccination was high or low; and the participant played as an elderly or young person.”<sup>147</sup>

Although the decision to obtain vaccination should be free from any undue influence, as the above analysis shows vaccination policies can be undermined. In order for vaccination programs to be effective, the free-riding behavior has to be taken into consideration. The free riding behavior is something that the authors of this report considered when developing guidelines for informed consent.

## 5.2. Informed Consent for Vaccination during translational/clinical vaccine research involving human participants

According to the Belmont Report, in order to respect the research subjects, there are two ethical principles that must be adhered to. The first principle is that individuals should be treated as autonomous agents. This will enable them to make decisions about their health only after being informed of what they are consenting to, while being free from the control of others. In the context of respecting the first principle of informed consent for vaccination research, requires that subjects be informed of all relevant details pertaining to their participation (i.e. project or vaccination objectives; what the research is about, how the research will be used, identity of researchers / clinicians; anticipated outcomes; and potential

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<sup>145</sup> Undue influence is a legal doctrine that involves one person taking advantage of a position of power over another person to exert his or her authority.

<sup>146</sup> Serpell L, Green J. Parental decision-making in childhood vaccination. *Vaccine*. 2006 May 8;24(19):4041-6.

<sup>147</sup> Ibuka Y, Li M, Vietri J, Chapman GB, Galvani AP. Free-riding behavior in vaccination decisions: An experimental study. *PloS one*. 2014 Jan 24;9(1):e87164.

risks and benefits, among other details) before making a decision as to whether or not to participate.<sup>148</sup>

The second principle is that individuals with diminished capacity are entitled to extra protection. In order to adhere to this principle, researchers must obtain consent from the patient, or someone who is legally authorized to provide informed consent on the patient's behalf. This individual is consenting on behalf of the patient only after being fully informed of all the risks and benefits.<sup>149</sup>

Based on our preliminary analysis of existing consent challenges (in the context of translational/clinical research), this report has identified the possible challenges that researchers face in obtaining informed consent from participants, particularly in regard to the second principle. There are two categories of challenges: those which are patient-centered and those which are process-centered.

### 5.3. Patient-Centered Barriers

For purposes of this report, the patient centered barriers are useful not only in formulating principles that deal with vaccination research, but also in formulating principles that deal with the administration of vaccines. Patient-centered barriers prevent a research subject from fully comprehending the disclosed information. While patients might initially feel comfortable with their participation in a vaccination research, they often become unsure of their involvement as the research progresses. This hesitation can result from a number of factors, including participants' mistrust of medical trial, perceived risk of harm, or inconvenience associated with the vaccine's protocol.

When working with vulnerable groups, patient-centered barriers include: developmental, illness-related and psychological/cultural factors. These will be discussed in further detail later in the report.

### 5.4. Process-Centered Barriers

Process-centered barriers, on the other hand, are useful in formulating principles that should be followed in translational/clinical vaccine research. Barriers beyond the mere signing of a consent form need to be addressed. These potential barriers include time issue - namely, the point during disease progression during which informed consent is sought.<sup>150</sup> Additionally, the period of time provided to patients to comprehend the information given to them by the

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<sup>148</sup> Sheehan M. Can broad consent be informed consent?. Public Health Ethics. 2011 Nov 1;4(3):226-35

<sup>149</sup> Taylor HA. Barriers to informed consent. In Seminars in oncology nursing 1999 May 1 (Vol. 15, No. 2, pp. 89-95). WB Saunders.

<sup>150</sup> For instance, some diseases may impact the patient's cognitive capacity at certain points of progression.

physician in order to make a decision can also play a factor. Finally, the content and readability of consent forms are also considered to be important barriers and need consideration.<sup>151</sup>

When working with vulnerable groups, process-centered barriers include various factors external to the patient. These will be discussed in further detail later in the report.

Therefore, there remains a need to identify key principles for overcoming these barriers to informed consent. We propose that such principles will serve as a foundational blueprint for obtaining informed consent in the context of research to give to patients a higher chance of maximizing their outcomes and avoiding harms.<sup>152</sup>

## 6. Privacy and Informed Consent

### 6.1. The EU General Data Protection Regulation

The European Union Data Protection law has been recently updated and will have a big impact for health care professionals, especially those involved in research. The General Data Protection Regulation (GDPR) has replaced the current legislation and will be implemented in May 2018, becoming a central role in the European Union regulation context.<sup>153</sup>

The GDPR has been added to be part of the Digital Single Market Strategy, partly because differences between EU members can contribute to ethics committees refusing to allow to the National Health Service (NHS) to transfer data to other EU countries.<sup>154</sup>

The main objectives of the GDPR are to remove barriers to the free movement of personal data information within different regions and to ensure the best and coherent protection for individuals. The GDPR in general will facilitate research, except for those cases not considered for the public interest. Harmonization will also be improved within the GDPR making international and European projects more easily feasible and ethically justifiable. Regarding the access of third parties to pseudonymized data, it still remains as an unresolved concern.<sup>155 156</sup>

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<sup>151</sup> Taylor HA. Barriers to informed consent. In Seminars in oncology nursing 1999 May 1 (Vol. 15, No. 2, pp. 89-95). WB Saunders.

<sup>152</sup> In particular, where participants' consent may be required to obtain, use, and share collected personal health information (i.e. in human tissue or data).

<sup>153</sup> Rumbold JMM, Pierscionek B. The effect of the General Data Protection Regulation on medical research. Journal of medical Internet research. 2017;19(2).

<sup>154</sup> Rumbold JMM, Pierscionek B. The effect of the General Data Protection Regulation on medical research. Journal of medical Internet research. 2017;19(2).

<sup>155</sup> Rumbold JMM, Pierscionek B. The effect of the General Data Protection Regulation on medical research. Journal of medical Internet research. 2017;19(2).

<sup>156</sup> Preite F, Salardi S, Gesuita R, Villani S, Trerotoli P, Guardabasso V, et al. The new european regulation on personal data protection: significant aspects for data processing for scientific research purposes. Epidemiology, Biostatistics and Public Health. 2017.



A balancing process within opposite rights is needed to consider by this Regulation. The right of the single person against the right of biomedical and scientific research when conducting clinical trials and publishing the results, and against the society interest to use those results to improve the quality of life of the community. Clearly, this is connected to what was discussed earlier when considering the individual versus communal conceptualization of autonomy. Hence, this balance need effective mechanisms to obtain informed consent in a way that preserves and takes into account both rights. It is necessary to consider it in the scope of the European legal system as it is founded on the protection of human rights and thus, on the values expressed by those rights. In other words, when a new directive or regulation is released it must comply not only with the legal requirements but also with the principles and values expressed by the legal system.<sup>157</sup>

Furthermore, investigators in some cases, have been able to identify research participants through public available information meaning that the data is easily identifiable in the networks. In this sense, it is important to consider the best approaches to protect and preserve the privacy rights of research subjects in this new era of digital information technology and data sharing. To reduce risks of re-identification, especially of genomic data, it has been broadly suggested the use of controlled access models where research databases are reviewed by committees that oversee the access requests.<sup>158 159</sup>

## 6.2. Regulation prospects in Biomedical Research

Provisions that have been identified to be applicable in the research and scientific field have been analyzed. Firstly, the regulation acknowledges that it is a good idea to couple information from registries, so investigators can obtain broader information from research results as it will involve a larger population. In this way, registries can provide solid results and high-quality knowledge improving therefore the community life. Regarding the anonymity of encoded data, it is clarified that those identities that can be traced with reasonable means, must be considered personal data to all effects.<sup>160</sup>

The term “pseudonymisation” refer to the data encoding operation when the personal data can no longer be related to a specific person unless additional information is provided, which is stored in a separate place. These data have identifiers replaced with a key code which can be

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<sup>157</sup> Preite F, Salardi S, Gesuita R, Villani S, Trerotoli P, Guardabasso V, et al. The new european regulation on personal data protection: significant aspects for data processing for scientific research purposes. *Epidemiology, Biostatistics and Public Health*. 2017.

<sup>158</sup> Compagnone C, Schatman ME, Rauck RL, Van Zundert J, Kraus M, Primorac D, et al. Past, Present, and Future of Informed Consent in Pain and Genomics Research: Challenges Facing Global Medical Community. *Pain Practice*. 2017;17(1):8-15.

<sup>159</sup> Shabani M, Borry P. Rules for processing genetic data for research purposes in view of the new EU General Data Protection Regulation. *European Journal of Human Genetics*. 2017:1.

<sup>160</sup> Preite F, Salardi S, Gesuita R, Villani S, Trerotoli P, Guardabasso V, et al. The new european regulation on personal data protection: significant aspects for data processing for scientific research purposes. *Epidemiology, Biostatistics and Public Health*. 2017.

used to trace the data back to an individual. According to GDPR, pseudonymized data must still be considered as personal data, because if the key code is hacked, all the data can be obtained. Truly anonymized data cannot be linked to an individual by any means.<sup>161</sup>

Another innovation of the new regulation is that consent for personal data processing is not applicable for deceased persons. Also, another important aspect in research is that at the time of data and tissue collection it is often not possible to know the specific purpose of the personal data processing for future scientific research, so it can be possible to use the data with subsequent purposes different from those initially declared. Also, when communication implies an existing risk to impair the achievement of the research purposes there is no need for consent.<sup>162</sup>

### 6.3. Data protection and ethical issues

Patient's consent nowadays goes beyond than just privacy or data protection. From an ethical point of view, it is a consequence of the principle of autonomy, one of the four pillars of medical ethics. In this way, a patient consent means that he or she decides autonomously to accept or not to undergo a treatment or his/her participation in a clinical trial. The discrepancies arise when research is done retrospectively: for example, on patient's tissues that have not been collected for research purposes, and it is doubtful whether a consent is needed.<sup>163</sup>

Current EU legislation varies across regions. There are some countries where patient consent is needed for any retrospective research, whereas other countries let patients to reject future research or even others that allow retrospective research without any consent. One of the general recommendations or comments widely discussed is that there should be a broad "one-time" consent, where patients allow their tissues to be processed for research purposes with the right to withdraw at any time. Thereby, investigators do not need to seek for re-consent every time, which is practically unfeasible, time-consuming, expensive and at times, intrusive into patient's lives, whether during their time alive or even well after they are deceased, but their advanced directives can allow for the use of their tissues. It is important that in this broad "one-time" consent patients will be informed about their tissues/data being used for future research as well as their storage conditions to safeguard their privacy, respecting then, the principle of autonomy, since the patient has the choice to consent and withdraw at any time.<sup>164</sup>

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<sup>161</sup> Rumbold JMM, Pierscionek B. The effect of the General Data Protection Regulation on medical research. *Journal of medical Internet research*. 2017;19(2).

<sup>162</sup> Preite F, Salardi S, Gesuita R, Villani S, Trerotoli P, Guardabasso V, et al. The new european regulation on personal data protection: significant aspects for data processing for scientific research purposes. *Epidemiology, Biostatistics and Public Health*. 2017.

<sup>163</sup> Casali P. Risks of the new EU data protection regulation: an ESMO position paper endorsed by the European oncology community. Oxford University Press; 2014.

<sup>164</sup> Casali P. Risks of the new EU data protection regulation: an ESMO position paper endorsed by the European oncology community. Oxford University Press; 2014.

## *The Principles of the Code of Conduct*

Regarding the use and transfer of residual tissue and data in research, there are three main principles of the Code of Conduct which state that:

- The residual tissue that can be used in an exchange program should be fully anonymized or anonymized but coded.<sup>165</sup>
- If this fully anonymized or anonymized but coded residual tissue is used, the minimum consent approach is to give the patient the option to opt-out.<sup>166</sup>
- The coordinating principle: the country of origin where the tissue was obtained from the patient and stored, is the one who decide if the tissue can be used in another country.<sup>167</sup>

Concerning rules of privacy, the Code of Conduct establish that:

Only data that is coded and tissue can be exchanged. The identity of the patient should never be disclosed by the researcher.<sup>168</sup>

## 6.4. What is privacy?

The concept of privacy was originally defined as the right to be let alone and excluding others to interfere in someone's private space. During the second half of the 21st century, technology and scientific development have grown in such a way that privacy has become to be easily invasive and the concept has been redefined. From the 1970s, the concept of privacy included also the right to control the use that others can make with our personal information. In other words, privacy has become the right to have control over one's own information and the mechanisms of construction of one's private space, including personality and identity.<sup>169</sup> There is not a unique widely accepted definition of privacy. Privacy could be "the ability to control the collection, use and disclosure of one's personal information"<sup>170</sup> but it can also be described taking into account whether others can see or have access to one's personal information.<sup>171</sup>

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<sup>165</sup> Van Veen E-B, Riegman P, Dinjens W, Lam K, Oomen M, Spatz A, et al. TuBaFrost 3: regulatory and ethical issues on the exchange of residual tissue for research across Europe. *European Journal of Cancer*. 2006;42(17):2914-23.

<sup>166</sup> Van Veen E-B, Riegman P, Dinjens W, Lam K, Oomen M, Spatz A, et al. TuBaFrost 3: regulatory and ethical issues on the exchange of residual tissue for research across Europe. *European Journal of Cancer*. 2006;42(17):2914-23.

<sup>167</sup> Van Veen E-B, Riegman P, Dinjens W, Lam K, Oomen M, Spatz A, et al. TuBaFrost 3: regulatory and ethical issues on the exchange of residual tissue for research across Europe. *European Journal of Cancer*. 2006;42(17):2914-23.

<sup>168</sup> Van Veen E-B, Riegman P, Dinjens W, Lam K, Oomen M, Spatz A, et al. TuBaFrost 3: regulatory and ethical issues on the exchange of residual tissue for research across Europe. *European Journal of Cancer*. 2006;42(17):2914-23.

<sup>169</sup> Preite F, Salardi S, Gesuita R, Villani S, Trerotoli P, Guardabasso V, et al. The new european regulation on personal data protection: significant aspects for data processing for scientific research purposes. *Epidemiology, Biostatistics and Public Health*. 2017.

<sup>170</sup> McGraw D, Greene SM, Miner CS, Staman KL, Welch MJ, Rubel A. Privacy and confidentiality in pragmatic clinical trials. *Clinical trials (London, England)*. 2015;12(5):520-9.

<sup>171</sup> McGraw D, Greene SM, Miner CS, Staman KL, Welch MJ, Rubel A. Privacy and confidentiality in pragmatic clinical trials. *Clinical trials (London, England)*. 2015;12(5):520-9.

Privacy can also be seen as the right of each individual to keep secret certain personality aspects, ideas, attitudes and/or behavior which are part of one's private life and he or she has the right not to communicate them to other people.<sup>172</sup>

Privacy is very important from a deontological point of view but also from the legal perspective as a guaranteed right. For this reason, protection of privacy, specifically, personal data protection is regulated by the European legal system.<sup>173</sup>

Investigators must ethically respect the privacy and confidentiality of their research participants. When identifiable information such as medical records, test results or other patient data is wished to be used by the investigator without the subject consent, there must be independent review boards and/or ethics committees that review the project and decide if the potential benefits outweigh the invasion of privacy. Patient representatives should also be included in these committees. Also, Institutional Review Boards (IRBs) must make sure that investigators are able to preserve the confidentiality of the patient's data. In order to minimize the risk of confidentiality breaches, some methods used to safeguard the confidentiality and protect the patient's privacy include replacing the names and other personal information with codes and storing the records in a secure place. These safeguards, should be adapted to new situations and work effectively despite of what type of consent the patient gives. When research results are published, patient identity is never disclosed as it is presented as summary results and aggregate information.<sup>174 175</sup>

#### 6.4.1. Medical Privacy requirements

It is necessary to consider confidentiality and privacy when collecting and storing tissues for a research purpose. In the USA, for instance, these issues are regulated by the Privacy of Individually Identifiable Health Information (Privacy Rule). The Privacy Rule requires specific written consent from a patient before any "protected health information" (PHI) is disclosed for research purposes. PHI, only refers to identifiable health information that is transmitted or maintained by a covered entity such as health care provider, health insurance plan or data processing firm. In this way, de-identified data is not PHI so a covered entity can release this kind of data without authorization as it is not subject of the Privacy Rule. The de-identified information, once coded, should not be allow for any derivable information about the patient, should not be possible to be translated so to identify the individual and the covering entity

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<sup>172</sup> Lemonidou C, Merkouris A, Leino-Kilpi H, Välimäki M, Dassen T, Gasull M, et al. A comparison of surgical patients' and nurses' perceptions of patients' autonomy, privacy and informed consent in nursing interventions. *Clinical Effectiveness in Nursing*. 2003;7(2):73-83.

<sup>173</sup> Preite F, Salardi S, Gesuita R, Villani S, Trerotoli P, Guardabasso V, et al. The new european regulation on personal data protection: significant aspects for data processing for scientific research purposes. *Epidemiology, Biostatistics and Public Health*. 2017.

<sup>174</sup> Casali P. Risks of the new EU data protection regulation: an ESMO position paper endorsed by the European oncology community. Oxford University Press; 2014.

<sup>175</sup> Kulynych J. Legal and ethical issues in neuroimaging research: human subjects protection, medical privacy, and the public communication of research results. *Brain and cognition*. 2002;50(3):345-57.

should not disclose the mechanism of re-identification.<sup>176</sup> Within EU Member States instead, the fundamental right to the protection of personal data is explicitly recognized in Article 8 of the Charter of Fundamental Rights of the European Union.<sup>177</sup>

#### 6.4.2. Personal and relational privacy

It is important to understand how informed consent is bounded to personal and relational privacy, especially in the context of an emerging field such as genetic medicine and research. When considering bioethical challenges raised by the new development of genetics medicine, two issues arise: informed consent and privacy. Normally, privacy and informed consent are understood at an individual level. However, genetic research goes beyond the individual because genetic findings may involve not only the individual person, but the family members or related persons at genetic risk. In this way, protection of data and confidentiality expands to a new concept of relational privacy and how the boundaries of relational and personal privacy are negotiated between patients and physicians that we have already addressed in chapter 3. The complexities of this kind of research have appeared as the development of new genetic medicine grows across different social and cultural contexts. Relational privacy becomes essentially relevant in the scope of storage of biological materials. The question of “who” is the patient in genetic medicine is a big issue, raising ethical considerations about the responsibility of the patients to their family members and to their physicians who need to address a right balance between the protection of privacy and confidentiality of the individual patient and the genetic risk to other members of the family. This balance becomes one of the most challenging aspects, because there is an ethical question between a person’s right to know, the right of others to not know, and the potential risks of information to the family. In this way, the decision of not sharing these kinds of information within the family or, in other words, the right to personal privacy, is not an act of “selfishness” but it could be the intention to protect others.<sup>178</sup>

#### 6.4.3. Privacy rights for adolescents

Adolescents are a specific vulnerable population between children and adults with obviously the same human rights and yet some specific developmental needs. In research, adolescents have often been excluded because there is an uncertainty regarding the ethical status and what should be the balance between protection from research and inclusion. Also, there is often confusion on who has the right and ability to give consent for them to participate in a clinical trial.<sup>179</sup>

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<sup>176</sup> Kapp MB. Ethical and legal issues in research involving human subjects: do you want a piece of me? *Journal of clinical pathology*. 2006;59(4):335-9.

<sup>177</sup> CHARTER OF FUNDAMENTAL RIGHTS OF THE EUROPEAN UNION.

<sup>178</sup> Goldim JR, Gibbon S. Between personal and relational privacy: understanding the work of informed consent in cancer genetics in Brazil. *Journal of Community Genetics*. 2015;6(3):287-93.

<sup>179</sup> Santelli J, Haerizadeh S, McGovern T, Unicef. Inclusion with Protection: Obtaining informed consent when conducting research with adolescents. 2017.

Privacy is also an existing issue regarding minors and adolescents since they cannot consent to research independently. It is true that the National Health Act does not specifically contemplate a minor's right to privacy. However, common law recognizes a child's right to privacy as the right of a person to keep aspects of their life private when it seems as reasonable by society. In this sense, adolescent research supposes a complex circumstance because it is uncertain when society regards as reasonable an adolescent's expectation of privacy. For instance, if an adolescent is positive to HIV infection in a trial, the adolescent may expect that the researcher keeps that information as confidential to his/her parents, because in general medicine, outside a clinical trial context, a person from the age of 14 can request the HIV testing and obtain the results confidentially. However, in the context of a clinical trial, parents give their consent to the participation of the adolescent, and given the case where regular HIV testing is part of the trial procedure and that the adolescent may need additional care and support if they get infected, it may seem as reasonable to ask the adolescent to share this information to a trusted adult and waive their privacy rights. Another example could be regarding sexual risk information, where adolescents expect to have their privacy rights and parents could be asked to waive their right to access this kind of information, when other safeguards are involved such as counselling and the information does not have a relevant risk. Recommendations on these issues include to have a balance and both parents and adolescents try to understand which information parents should have access to or not.<sup>180</sup>

## 6.5. Privacy vs Transparency

Sharing clinical trial data and clinical trial results seems to be significantly important for the community to enhance research and increase transparency. It is believed that patients have the right to know about the scientific basis of the approved medicines they are going to use and hence, transparency of the clinical trial data is crucial. However, how to implement the principle of transparency while respecting the privacy of personal data and confidential information remains still a delicate matter. As broader use of clinical data in academia and research institutes can enhance unbiased analysis of the results, advanced science research and can also help regulators to decide; patient's privacy must be always protected by appropriate policies and technological procedures, especially in cases where the disease of study is a rare disease, where the risk to identify the patient is higher.<sup>181</sup>

*Informed Consent Process: trust, respect, privacy, autonomy and confidentiality.* The informed consent process begins when the first contact between a potential subject and the researcher is established and it continues throughout the monitoring and follow up phase. This process requires having an appropriate environment and enough time to discuss and review the written

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<sup>180</sup> Slack C, Strode A, Fleischer T, Gray G, Ranchod C. Enrolling adolescents in HIV vaccine trials: reflections on legal complexities from South Africa. BMC Medical Ethics. 2007;8(1):5.

<sup>181</sup> Bonini S, Eichler H-G, Wathion N, Rasi G. Transparency and the European Medicines Agency—sharing of clinical trial data. New England Journal of Medicine. 2014;371(26):2452-5.

document with the patients, their families and friends and provide also sufficient time for asking questions.<sup>182</sup>

The informed consent is the main tool to generate trust and improve the physician-patient relationship. This tool pretends to protect patient interests, which is crucial in research and clinical practice. It also includes the main ethical rules that model the medical responsibility, that results from the application of the principle of dignity, the principle of respect for autonomy and trust in people, as well as the confidentiality and veracity rules. Informed consent is also used to request people's permission that are exposed to medical treatment or procedures, in order to respect their individual dignity.<sup>183</sup>

The physician-researcher that takes part in a clinical trial has a double role: on one hand, he or she is the physician responsible for the physical, mental and social well-being of the patient, and on the other hand, he or she is the researcher responsible for the correct conduct of the trial. Consequently, he or she has to comply with the principle of non-maleficence and take into account that the patient's protection is more important than the scientific benefit of the research or their personal and professional interests as investigators.<sup>184</sup>

Whenever a researcher collects information from a human participant or analyzes identifiable records, he or she needs to comply with all the obligations of "human research protection", which is a necessary first step towards a responsible conduct of research. The investigator need to ensure that the participation of subjects is fully informed and voluntary.<sup>185</sup>

## 6.6. Principle of respect

The principle of respect is related to the concept of autonomy, where individuals are able to make their own decisions about their lives. Health information is considered particularly sensible and personal. In this way, privacy in health information is a component of the principle of respect, where this type of information should only be shared under reasonable conditions and parties and will not be used or disclosed inappropriately.<sup>186</sup>

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<sup>182</sup> Altamirano Bustamante N, Altamirano Bustamante E, Olaya Vargas A, Rubens Jd, García de la Puente S, Altamirano Bustamante MM. Consentimiento informado en grupos vulnerables: participación de niños y adolescentes en protocolos de investigación. Boletín médico del Hospital Infantil de México. 2010;67(3):248-58.

<sup>183</sup> Altamirano Bustamante N, Altamirano Bustamante E, Olaya Vargas A, Rubens Jd, García de la Puente S, Altamirano Bustamante MM. Consentimiento informado en grupos vulnerables: participación de niños y adolescentes en protocolos de investigación. Boletín médico del Hospital Infantil de México. 2010;67(3):248-58.

<sup>184</sup> Altamirano Bustamante N, Altamirano Bustamante E, Olaya Vargas A, Rubens Jd, García de la Puente S, Altamirano Bustamante MM. Consentimiento informado en grupos vulnerables: participación de niños y adolescentes en protocolos de investigación. Boletín médico del Hospital Infantil de México. 2010;67(3):248-58.

<sup>185</sup> Kulynych J. Legal and ethical issues in neuroimaging research: human subjects protection, medical privacy, and the public communication of research results. Brain and cognition. 2002;50(3):345-57.

<sup>186</sup> McGraw D, Greene SM, Miner CS, Staman KL, Welch MJ, Rubel A. Privacy and confidentiality in pragmatic clinical trials. Clinical trials (London, England). 2015;12(5):520-9.

### *Strategies and recommendations to protect privacy interests and promote research*

Future research purposes often involve the issue of obtaining or not a re-consent for the use of confidential clinical information. How to protect privacy interests of the participants while promoting at the same time the future of research is unescapable big challenge. Dynamic informed consent seems to be one of the solutions best proposed, although if not possible, at least certain recommendations should be considered:<sup>187</sup>

- Participants should receive regular notifications of results and updates regarding the clinical trial.<sup>188</sup>
- Patients participation should be promoted at a more institutional level by involving patient associations and applied and developed with appropriate policies.<sup>189</sup>

Regarding re-consent, the IRB should provide guidance for researchers and a careful evaluation of some elements should be done in order to make the decision of asking or not for re-consent. These elements include the possibility of re-contact the patients depending also on the researcher's reasonable effort, resources and availability of contact details, and so on.<sup>190</sup>

There is a need to implement legal provisions to protect the confidentiality by reviewing the mechanisms to well understand the retrospective researches as well as supporting full transparency and appropriate storage of patient tissues and health data.<sup>191</sup>

For instance, the European Cancer community requests all the EU decision makers to save research results but protecting the patient's right to donate their data and tissues in order to find new treatments. In this way, the revision of the new Data Protection Directive might be able to consider a balance between the right to privacy and the right to health that can be

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<sup>187</sup> Gainotti S, Turner C, Woods S, Kole A, McCormack P, Lochmüller H, et al. Improving the informed consent process in international collaborative rare disease research: effective consent for effective research. *European Journal of Human Genetics*. 2016;24(9):1248.

<sup>188</sup> Gainotti S, Turner C, Woods S, Kole A, McCormack P, Lochmüller H, et al. Improving the informed consent process in international collaborative rare disease research: effective consent for effective research. *European Journal of Human Genetics*. 2016;24(9):1248.

<sup>189</sup> Gainotti S, Turner C, Woods S, Kole A, McCormack P, Lochmüller H, et al. Improving the informed consent process in international collaborative rare disease research: effective consent for effective research. *European Journal of Human Genetics*. 2016;24(9):1248.

<sup>190</sup> Gainotti S, Turner C, Woods S, Kole A, McCormack P, Lochmüller H, et al. Improving the informed consent process in international collaborative rare disease research: effective consent for effective research. *European Journal of Human Genetics*. 2016;24(9):1248.

<sup>191</sup> Casali P. Risks of the new EU data protection regulation: an ESMO position paper endorsed by the European oncology community. Oxford University Press; 2014.



obtained by addressing all concerns while accomplishing those related to privacy and ethical use of personal health information.<sup>192 193</sup>

There are a lot of approaches to balance the protection of privacy while facilitating the research. Some members of the research community suggest having access to confidential data without a strong privacy protection just based on their belief of being trusted and qualified persons that will preserve patients' rights. Other recommendations suggested by Simon and others are the following:<sup>194</sup>

- Informed consent should be asked to access to patient's data when there is a clear intention at the time of collecting the medical information to use it for research purposes.<sup>195</sup>
- A review by an IRB, should be required in those cases where investigators request access to medical information not collected for research purposes, to determine if the criteria for waiving consent is met. In these cases, the investigator will need to demonstrate the need of those data to conduct the research, the minimum risk for the subject's privacy, and the maximum protection of patient's privacy by using identifier codes and the use of the minimum information required.<sup>196</sup>
- Rigorous penalties for misuse of research data.<sup>197</sup>

Regarding different mechanisms for honoring privacy interests and autonomy, there are existing initiatives, such as the Patient-Centered Outcomes Research Institute's (PCORI) National Patient Centered Outcomes Research Network (PCORnet) and the National Institutes of health (NIH) Health Systems Research Collaboratory (Collaboratory); where they are performing ways and methodologies beyond informed consent to protect the privacy and autonomy of the research participants. Innovative examples of approaches to respect the autonomy and rights of subjects without relying only on individual consent are:<sup>198</sup>

- Greater input into research and research policies:

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<sup>192</sup> Casali P. Risks of the new EU data protection regulation: an ESMO position paper endorsed by the European oncology community. Oxford University Press; 2014.

<sup>193</sup> Di Iorio C, Carinci F, Oderkirk J. Health research and systems' governance are at risk: should the right to data protection override health? Journal of medical ethics. 2014;40(7):488-92.

<sup>194</sup> Appelbaum PS. Protecting privacy while facilitating research. American Journal of Psychiatry. 2000;157(11):1725-6.

<sup>195</sup> Appelbaum PS. Protecting privacy while facilitating research. American Journal of Psychiatry. 2000;157(11):1725-6.

<sup>196</sup> Appelbaum PS. Protecting privacy while facilitating research. American Journal of Psychiatry. 2000;157(11):1725-6.

<sup>197</sup> Appelbaum PS. Protecting privacy while facilitating research. American Journal of Psychiatry. 2000;157(11):1725-6.

<sup>198</sup> McGraw D, Greene SM, Miner CS, Staman KL, Welch MJ, Rubel A. Privacy and confidentiality in pragmatic clinical trials. Clinical trials (London, England). 2015;12(5):520-9.

PCORI was first created to help patients, health care professionals, and stakeholders to make better and informed health-care decisions as well as improve the scientific evidence. PCORnet aims to improve patient outcomes by connecting patients, clinicians, researchers and health systems. It includes 29 sites, 18 of which are patient-powered networks and 11 are clinical data research networks. These networks have individually their own approaches to engage research participants. However, there is a PCORnet Patient Council (PPC) that develops policies and best practices and provide them to the PCORnet, acting as a patient advisory group. The Collaboratory Stakeholder Engagement Core acts also as an advisory group and is formed by patient and consumer representatives. They give feedback focus on the study design and implementation issues and their suggested approach is to collaborate and partner with stakeholders.<sup>199</sup>

#### ● Opt out:

When an informed consent is signed, the participant “opt in” to a clinical trial. The “opt out” model is when the participant is included automatically, unless they opt out. This opt out can be complete or with restrictions when some data is allowed to be used.<sup>200</sup>

#### ● Broad Notification:

This approach provides information through posters, emails, social media, brochures or web portals that protect autonomy and informs about the procedure of the trial and the rationale for why it is being conducted. It is indicated for minimal risk studies, where a broad notification may be enough to protect autonomy. This approach does not seek consent, but even when a waiver of consent is granted it is ethically appropriate to inform, showing respect for participant interests and autonomy.<sup>201</sup>

#### ● Individual Notification:

This approach increases transparency by ensuring that patients are well informed about the research they are involved in. It is important to notify and inform every patient about the trial sponsor, the purpose of the trial, the transmission of patient data, the safety of the procedures and other aspects -even when a waiver of consent is granted. In this way, patient’s interests are being respected and their autonomy is being preserved by offering also a way for opting out if they want to.<sup>202</sup>

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<sup>199</sup> McGraw D, Greene SM, Miner CS, Staman KL, Welch MJ, Rubel A. Privacy and confidentiality in pragmatic clinical trials. *Clinical trials* (London, England). 2015;12(5):520-9.

<sup>200</sup> McGraw D, Greene SM, Miner CS, Staman KL, Welch MJ, Rubel A. Privacy and confidentiality in pragmatic clinical trials. *Clinical trials* (London, England). 2015;12(5):520-9.

<sup>201</sup> McGraw D, Greene SM, Miner CS, Staman KL, Welch MJ, Rubel A. Privacy and confidentiality in pragmatic clinical trials. *Clinical trials* (London, England). 2015;12(5):520-9.

<sup>202</sup> McGraw D, Greene SM, Miner CS, Staman KL, Welch MJ, Rubel A. Privacy and confidentiality in pragmatic clinical trials. *Clinical trials* (London, England). 2015;12(5):520-9.

## ● Community Consultation:

Community consultation is an approach where people agree to be controlled by the community representative's decisions in terms of research uses.<sup>203</sup>

Other recommendations regarding the protection of privacy at the same time as promoting research that should be taken into account in the informed consent process are:

- Hospitals and other institutions active in research should inform patients that their medical records may be used to identify them as potential subjects for clinical trials, being possibly contacted, but with a written opt out possibility.<sup>204</sup>
- Wording of the informed consent should consider the fact of continued use of information from participants, even after they withdraw from the procedures.<sup>205</sup>
- In studies where a long-term follow up is anticipated known, it should be mentioned in the consent form with a statement affirming that confidential identifiable information may be held.<sup>206</sup>

Effective strategies to balance collection and management of medical records and privacy protection also include modern technology, which consists on developing an electronic healthcare privacy protection tool that complies with the regulation requirements at the same time that provides access to data to both investigators and health care organizations. However, apart from technological approaches, a decisive solution to the challenge of conducting effective research within the scope of healthcare data protection might only be possible if all stakeholders take a common perspective towards health information usage. In this way, patients, health care providers, government and investigators should consider the use of medical records not only as a potential risk to individual autonomy and privacy but also as a crucial element to provide the best clinical research and medical care.<sup>207</sup>

Other approaches to better protect medical and research data are:

- Limit the access to the minimum staff necessary.<sup>208</sup>

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<sup>203</sup> McGraw D, Greene SM, Miner CS, Staman KL, Welch MJ, Rubel A. Privacy and confidentiality in pragmatic clinical trials. *Clinical trials* (London, England). 2015;12(5):520-9.

<sup>204</sup> Armitage J, Souhami R, Friedman L, Hilbrich L, Holland J, Muhlbaier LH, et al. The impact of privacy and confidentiality laws on the conduct of clinical trials. *Clinical trials*. 2008;5(1):70-4.

<sup>205</sup> Armitage J, Souhami R, Friedman L, Hilbrich L, Holland J, Muhlbaier LH, et al. The impact of privacy and confidentiality laws on the conduct of clinical trials. *Clinical trials*. 2008;5(1):70-4.

<sup>206</sup> Armitage J, Souhami R, Friedman L, Hilbrich L, Holland J, Muhlbaier LH, et al. The impact of privacy and confidentiality laws on the conduct of clinical trials. *Clinical trials*. 2008;5(1):70-4.

<sup>207</sup> Rosano G, Pelliccia F, Gaudio C, Coats AJ. The challenge of performing effective medical research in the era of healthcare data protection. *International journal of cardiology*. 2014;177(2):510-1.

<sup>208</sup> Compagnone C, Schatman ME, Rauck RL, Van Zundert J, Kraus M, Primorac D, et al. Past, Present, and Future of Informed Consent in Pain and Genomics Research: Challenges Facing Global Medical Community. *Pain Practice*. 2017;17(1):8-15.

- Include privacy and security safeguards to all parties that hold the identifiable health information such as internet service providers, website, device developers, mobile application.<sup>209</sup>
- Data sharing should go beyond the federal requirements and use protections such as encryption, virtual private networks, tests for network threats and so on. In fact, there are methods where one could allow access to a secondary user to analyze data without downloading it.<sup>210</sup>
- Technical approaches that aggregates the information and alters some values in a data set so that the data set is still useful for group analysis, but individual privacy re-identification is better protected.<sup>211</sup>
- Include a committee with patient representatives who can address public concerns, that oversights the organizations that collects and stores the confidential health information.<sup>212</sup>

## 7. Informed Consent for Vulnerable Groups: Priority Needs and Specific Principles

By placing emphasis on three specific vaccination case studies (namely, the novel meningitis, Respiratory Syncytial Virus (RSV), and Human Papilloma Virus (HPV) vaccines), this report wants to highlight how vulnerable groups (specifically preadolescents, adolescents, and pregnant women) require additional considerations beyond the general principles discussed above. Under this section the report initially discusses a proposed framework when assessing informed consent in vulnerable populations. This framework will then be applied to the vulnerable groups that the report focuses on, with emphasis on each group's specific needs. Following that discussion, the report will propose principles that should be implemented to improve the administration of these three particular vaccines (meningitis, RSV, and HPV) to members of the vulnerable groups that are considered here.

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<sup>209</sup> Lo B, Goodman SN. Sharing clinical research data—finding the right balance. JAMA internal medicine. 2017;177(9):1241-2.

<sup>210</sup> Lo B, Goodman SN. Sharing clinical research data—finding the right balance. JAMA internal medicine. 2017;177(9):1241-2.

<sup>211</sup> Lo B, Goodman SN. Sharing clinical research data—finding the right balance. JAMA internal medicine. 2017;177(9):1241-2.

<sup>212</sup> Lo B, Goodman SN. Sharing clinical research data—finding the right balance. JAMA internal medicine. 2017;177(9):1241-2.

## 7.1. A Framework for Additional Ethical Considerations in Dealing with Vulnerable Groups

### 7.1.1. Defining vulnerability. What makes a participant vulnerable?

The definition of vulnerable generally has the same meaning of risk. A group is usually vulnerable because the individuals in the group suffer multiple or intersectional discrimination. Below is a list of examples of individuals, groups, societies and populations classified as particularly vulnerable in research ethics guidelines and declarations.

The Belmont Report (1979):

- Ethnic minorities
- Economically disadvantaged
- Terminally ill
- Persons confined to institutions

The Declaration of Helsinki (2009)

- Subjects unable to give informed consent
- Subjects receptive to coercion or undue influence
- Populations or societies that will not benefit directly from participation in research
- Patients who participate in medical research in combination with medical treatment and care

CIOMS (2002)<sup>213</sup>

- Persons unable to give informed consent
- Children
- Junior or subordinate members of a hierarchical group (e.g. medical students, nursing students, subordinate health and laboratory personnel at hospitals, employees of pharmaceutical companies, military personnel and the police)
- The elderly
- Residents of retirement and nursing home
- People receiving welfare benefits or social assistance

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<sup>213</sup> CIOMS (Council for International Organizations of Medical Sciences) 2002: International Ethical Guidelines for Biomedical Research Involving Human Subjects.

- Poor persons
- The unemployed
- Patients in emergency rooms
- Some ethnic minorities
- The homeless
- Nomads
- Refugees and asylum-seekers
- Prisoners
- Patients with incurable disease
- Politically powerless individuals
- Members of communities unfamiliar with modern medical concepts

For the topic that concerns us here the ICH GCP definition of vulnerable participants at clinical trials is as follows: “Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include participants with incurable diseases, persons in nursing homes, unemployed or impoverished persons, those in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.”<sup>214</sup>

So, vulnerable groups include the person who is absolutely or relatively incapable of protecting their interests. Obtaining informed consent is critical when working with them, specifically with some groups like people with learning disabilities. There may be potential problems of understanding what the research is about, what their role in the research will be and how the research will be used.<sup>215</sup> There is a presumption that vulnerable groups are especially susceptible to being unduly influenced into providing consent, and therefore have a rightful claim to special consideration or protection. For instance, a group is generally considered to be vulnerable when they have a “compromised ability to protect their interests and provide informed consent.”<sup>216</sup> However, providing any meaningful ethical guidance to informed

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<sup>214</sup> Guideline for Good Clinical Practice.

<sup>215</sup> Ethical Principles for Researching Vulnerable Groups, 2003.

<sup>216</sup> Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton JA. Enrolling pregnant women: issues in clinical research. *Women's Health Issues*. 2013 Feb 28;23(1):e39-45.

consent challenges in the context of our target groups necessitates defining the essential traits and scope of vulnerable persons or populations.<sup>217</sup> More precisely, understanding the concept of vulnerability is key to understanding the consent challenges in the context of vaccination cases and clinical research, through both a gendered lenses and the impact it has on young individuals. A common pattern in international declarations and ethical guidelines of defining vulnerability is to focus solely on particular populations, for example women, children or ethnic minorities. This pattern has been criticized as it may lead to the implication that individuals who are members of these populations are inherently vulnerable in all situations (e.g. vulnerability in all cases of vaccination or clinical research).<sup>218</sup> In this regard, the National Bioethics Advisory Commission (NBAC) has argued that “vulnerability is sensitive to context and individuals may be vulnerable in one situation but not in another.”<sup>219</sup> In other words, the NBAC has suggested that vulnerability should be defined in terms of situations in which individuals might be considered vulnerable, rather than in terms of particular groups or populations. For example, where gender intersects with poverty, it would exacerbate the social vulnerabilities faced by women belonging to this group. However, such categorization does not prove that our target group is necessarily vulnerable in all cases of vaccination and clinical research.<sup>220</sup>

As a procedural solution to accommodate the needs of our target group, the model of informed consent in itself must firstly be defined. Specifically, meaningful ethical guidance (for informed consent challenges involving children, adolescents, and pregnant women) requires clarification regarding what the “informed” criterion for consent in law and policy substantively entails. Informed consent must be given voluntarily, and this voluntarism can be diminished by factors such as “developmental immaturity, cognitive deficits, illness, and pressures present in certain settings.”<sup>221</sup> In such instances, it is important that the consent obtained by the physicians is without undue influence or coercion. Physician coercion refers to the undue influence that a physician can exert on a patient when the patient is required to make a decision. Physician need to involve patient in the study design and promote continuous consent asking what patients think, what they need, and what they want to truly ensure the informed consent is patient-centered. Indeed, power relationships, such as those between physicians and women or racial

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<sup>217</sup> Iltis A. Introduction: Vulnerability in Biomedical Research. *The Journal of Law, Medicine & Ethics*. 2009;37(1):6-11.

<sup>218</sup> Wang Y. *Human Population Genetic Research in Developing Countries: The Issue of Group Protection*. Routledge; 2013 Nov 12.

<sup>219</sup> Commission N. *Ethical and Policy Issues in Research Involving Human Participants* [Internet]. Scholarworks.iupui.edu. 2017 [cited 5 March 2018]. Available from: <https://scholarworks.iupui.edu/handle/1805/25>

<sup>220</sup> In terms of a more situationally defined conception of vulnerability, we may seek guidance from the United States (U.S.) federal government, which identifies — via a context-sensitive approach — specific populations given extra protection in the *Code of Federal Regulations (CFR)*: these include pregnant women, human fetus and neonates, prisoners, and children, among other groups. Although the CFR does not present us with an exhaustive list of vulnerable populations, what is provided is a concept of vulnerability that is based upon: ability to consent; risk and reward in the study; potential for coercion; and choice of subjects.

<sup>221</sup> Roberts LW. Informed consent and the capacity for voluntarism. *American Journal of Psychiatry*. 2002 May 1;159(5):705-12.

minorities, have also been shown to impact a person’s ability to decline courses of treatment.<sup>222</sup> Thus, this report proposes that in order to obtain informed consent, vaccinators might not only provide sufficient information, but also make sure that they are not unduly coercing the patient into accepting the vaccines, listening them to facilitate effective treatment planning.

Our proposed framework incorporates several additional principles that are categorized as either process or patient-centered barriers.

### 7.1.2. Model of Informed Consent for Vulnerable Groups

When working with vulnerable groups, the consent provided has four additional considerations. These are: developmental factors, illness-related considerations, psychological issues and cultural values, and external pressure.<sup>223</sup> These in turn can be related to eight traits of vulnerability identified by the Institutional Review Board for Social and Behavioral Sciences (IRB-SBS) at the University of Virginia.<sup>224</sup>

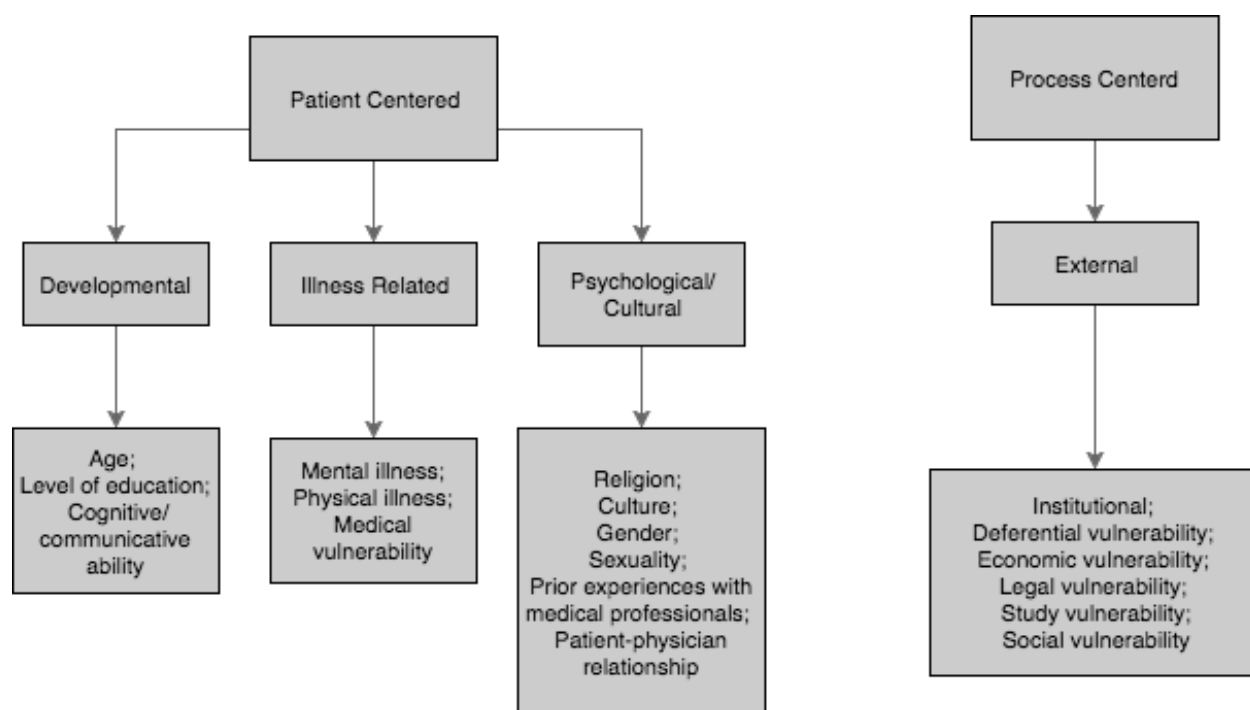


Figure 1: Patient and Process Centered Barriers

<sup>222</sup> Roberts LW. Informed consent and the capacity for voluntarism. American Journal of Psychiatry. 2002 May 1;159(5):705-12.

<sup>223</sup> Roberts LW. Informed consent and the capacity for voluntarism. American Journal of Psychiatry. 2002 May 1;159(5):705-12.

<sup>224</sup> The University of Virginia has identified eight traits of vulnerability that may interfere with an individual’s ability to protect themselves in research or clinical interventions—especially during the informed consent process.



### *Developmental Factors*

Development in the form of “cognitive ability, emotional maturity, and moral character” all have an impact on the voluntariness of the consent provided.<sup>225</sup> Cognition is integral to voluntariness, as patients must understand the significance and the impact of their consent.<sup>226</sup> Having the capacity to provide informed consent includes the abilities of “(understanding), logical reasoning, communicating a well-reasoned choice, and appreciating the significance of the decision made.”<sup>227</sup> Cognitive or communicative vulnerability means that the participant is unable to process, understand, appreciate, and reason through the consent documentation and/or explanations, due to either mental or language limitations. For example, the developmental capacity of children must be considered, and their ability to make decisions must be differentiated from their ability to make informed decisions regarding their health.

Age and level of education have both been shown to have detrimental impacts on a patient’s comprehension in the informed consent process. In particular, the ability to read is central to capacity for providing informed consent. Excessive length and complex language reduces the comprehensibility of consent forms.<sup>228</sup> Furthermore, a deficiency in mental ability means patients are providing consent without fully understanding the risks associated with their participation.<sup>229 230 231</sup>

### *Illness-Related Considerations*

Mental and physical illnesses are detrimental factors, in that they diminish the quality of consent. This includes individuals whose medical state may cloud their ability or judgment to make an informed decision regarding study participation. For instance, a patient that perceives a research study as a miracle cure to their disorder rather than a procedure that may have no guarantee for results. The presence of the symptoms of an illness may hinder an individual’s ability to ensure that their motivations for providing consent are appropriate.<sup>232</sup> However, the

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<sup>225</sup> Roberts LW. Informed consent and the capacity for voluntarism. *American Journal of Psychiatry*. 2002 May 1;159(5):705-12.

<sup>226</sup> Escobedo C, Guerrero J, Lujan G, Ramirez A, Serrano D. Ethical issues with informed consent. *Elizabeth Zubiate*. 2007;8:1-44

<sup>227</sup> Gupta UC, Kharawala S. Informed consent in psychiatry clinical research: A conceptual review of issues, challenges, and recommendations. *Perspectives in clinical research*. 2012 Jan 1;3(1):8.

<sup>228</sup> Albala I, Doyle M, Appelbaum PS. The evolution of consent forms for research: a quarter century of changes. *IRB: Ethics & Human Research*. 2010 May 1;32(3):7-11.

<sup>229</sup> Furthermore, the presence of any pre-existing illness may risk exposing associated psychological problems that would impact a patient’s autonomy and their ability to provide informed consent.

<sup>230</sup> Gupta UC, Kharawala S. Informed consent in psychiatry clinical research: A conceptual review of issues, challenges, and recommendations. *Perspectives in clinical research*. 2012 Jan 1;3(1):8.

<sup>231</sup> Taylor HA. Barriers to informed consent. *In Seminars in oncology nursing* 1999 May 1 (Vol. 15, No. 2, pp. 89-95). WB Saunders.

<sup>232</sup> Roberts LW. Informed consent and the capacity for voluntarism. *American Journal of Psychiatry*. 2002 May 1;159(5):705-12.

presence of a mental disorder must not be likened with the incapacity to make an informed decision about a medical treatment. A patient with mental illness therefore is presumed capable of consenting to treatment or research until sufficient evidence to the contrary is demonstrated.<sup>233</sup>

### *Psychological and Cultural/Religious Values*

A patient's cultural disposition and past experiences with medical health care professionals will have an impact on the amount of trust that they can have in a vaccine's efficacy. Although local culture may shape people's perception over time, people are more likely to trust experts that share a similar culture with them.<sup>234</sup> When working with ethnic minority patients, it is important to note that comprehension may also transcend simply linguistic barriers. The conceptualization of illness and cultural bias both play a role in the ways that information is presented and understood. Thus, it is important to understand the role that culture plays in obtaining informed consent.<sup>235</sup> In particular, in multicultural societies, where a large portion of the society is made up of immigrants with varying cultural backgrounds, there may be differing attitudes regarding the role of physicians.

### *External Factors*

There are further external systemic vulnerabilities that can impact the consent obtained from a patient. The following is a non-exhaustive overview of such factors.

Institutional vulnerability is an external factor whereby individuals are *formally* subordinated to an authority figure and their consent may be coerced either directly or indirectly. Examples include prisoners, student/teacher relationships, or employee/employer relationships.

Deferential vulnerability includes individuals that are *informally* subordinated to an authority figure and who may feel obligated to follow advice (such as to consent) proceeding from such authority. For example, abuse victims, doctor/patient relationships, or husband/wife relationships.

Economic vulnerability includes individuals whose economic situation may make them vulnerable to the prospect of free medical care and/or the payments issued for participating in a study;

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<sup>233</sup> Grisso T, Appelbaum PS. Assessing competence to consent to treatment: A guide for physicians and other health professionals. Oxford University Press, USA; 1998.

<sup>234</sup> Kahan DM, Braman D, Cohen GL, Gastil J, Slovic P. Who fears the HPV vaccine, who doesn't, and why? An experimental study of the mechanisms of cultural cognition. *Law and human behavior*. 2010 Dec 1;34(6):501-16.

<sup>235</sup> Dein S, Bhui K. Issues concerning informed consent for medical research among non-westernized ethnic minority patients in the UK. *Journal of the Royal Society of Medicine*. 2005 Aug 1;98(8):354-6.

Legal vulnerability includes participants that do not have the legal right to consent or those concerned that their consent could put them at risk for legal repercussions (e.g. forfeiture of health insurance coverage due to potential associated risks of genetic discrimination).

Lastly, there is social vulnerability, which includes individuals that are at risk for discrimination based upon race, gender, ethnicity, and/or age. For example, physicians or researchers may not offer the full explanation in the consent owing to prejudicial attitudes against females or because they presume that the individual under their care is not able to comprehend the information due to young age. Furthermore, the ways in which race plays a role in asymmetrical power relationships between a patient and physician must also be considered.<sup>236</sup> Physicians may unintentionally reiterate racial bias into their practice and they may also lack cultural competency in understanding the patient's comprehension of illness.<sup>237</sup>

The traits most relevant to our target group, and which therefore warrant our consideration, are: cognitive or communicative; social; and legal vulnerabilities. Later in the chapter some proposals on how to avoid the specific consent barriers presented by these three vulnerability traits among young people and pregnant women will be taken into account.

## 7.2. Vaccination Involving Vulnerable Groups: Preadolescents, Adolescents, Pregnant Women, and Their Specific Needs

The informed consent process poses several ethical challenges since failures of informed consent may result in the violations of individuals' human rights. Diverse factors, ranging from poverty, disease, lack of education, hardship and submissiveness, to the effects of war, famine, pandemics, and social insecurity, all play a role in making participants and patients more vulnerable to research exploitation.<sup>238</sup> Such factors must therefore be considered by clinicians and researchers alike in their efforts to seek informed consent, especially among vulnerable groups.<sup>239 240</sup>

Patient-physician communication is integral to "building a therapeutic doctor-patient relationship."<sup>241</sup> Effective communication plays a large role in regulating a patient's emotions, aiding in the comprehension of medical information by the patient, and a better identification of patient's perceptions and expectations. Furthermore, the patient-physician relationship

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<sup>236</sup> Dein S, Bhui K. Issues concerning informed consent for medical research among non-westernized ethnic minority patients in the UK. *Journal of the Royal Society of Medicine*. 2005 Aug 1;98(8):354-6.

<sup>237</sup> Cooper-Patrick L, Gallo JJ, Gonzales JJ, Vu HT, Powe NR, Nelson C, Ford DE. Race, gender, and partnership in the patient-physician relationship. *Jama*. 1999 Aug 11;282(6):583-9.

<sup>238</sup> Wang Y. *Human Population Genetic Research in Developing Countries: The Issue of Group Protection*. Routledge; 2013 Nov 12.

<sup>239</sup> E.g. Lower literacy rates and minority status have both been shown to be determinants of comprehension in providing consent

<sup>240</sup> Grisso T, Appelbaum PS. *Assessing competence to consent to treatment: A guide for physicians and other health professionals*. Oxford University Press, USA; 1998.

<sup>241</sup> Ha JF, Longnecker N. Doctor-patient communication: a review. *The Ochsner Journal*. 2010 Mar;10(1):38-43.

must be understood in the context of historical and social (race, socioeconomic status, education, gender) relationships between the two parties.<sup>242</sup>

The patient-physician relationship is at constant odds between the need to provide the physician the full decision-making power, and to provide patients with the autonomy over their treatment decisions. Control must be shared, particularly when working with vulnerable populations, in order to transform the relationship into a partnership.<sup>243</sup>

### 7.2.1. Children

Informed consent rests on the notion that a patient comprehends the nature of the treatment and his or her rights with respect to the treatment. In ethics and law, minors are presumed to lack the ability to understand the nature of such decisions because of lesser developed cognitive functions and power differentials within the patient-physician relationship.<sup>244</sup>

For children under the age of 18, consent/permission to participate in a clinical trial has to be obtained from parents. In the case of minors, Principle 11 of the Declaration of Helsinki stipulates that ‘permission from the responsible relative replaces that of the subject in accordance with national legislation’.

If the child is above 7 years of age, then “child assent” is also mandatory. It can be argued that children have rights to receive information, to be listened to, have their wishes and feelings taken into account and to give or withhold consent if judged competent to do so. Difficulty arises when parents give their consent while the child refuses to assent. Attitudes towards children’s participation in health care decision making may impact decisions about their clinical trial participation.<sup>245</sup>

The decision-making capacity in children varies, depending on the age, circumstances, mental status, and the risks associated with their decision. The ability of children to provide consent develops as they mature, and thus developmental factors play a large role in addressing the validity of their informed consent.

It becomes important to differentiate between the cognitive functions and social experiences of the age groups of minors. Preadolescent children should be excluded from providing meaningful consent, whereas adolescents 14 years old and above can participate in their treatment decision-making in more concrete ways. In Piaget’s four stages of intellectual

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<sup>242</sup> Ellingson LL, Buzzanell PM. Listening to women's narratives of breast cancer treatment: A feminist approach to patient satisfaction with physician-patient communication. *Health Communication*. 1999 Apr 1;11(2):153-83.

<sup>243</sup> Ellingson LL, Buzzanell PM. Listening to women's narratives of breast cancer treatment: A feminist approach to patient satisfaction with physician-patient communication. *Health Communication*. 1999 Apr 1;11(2):153-83.

<sup>244</sup> Bruzzese JM, Fisher CB. Assessing and enhancing the research consent capacity of children and youth. *Applied Developmental Science*. 2003 Jan 1;7(1):13-26.

<sup>245</sup> Coyne I, O'Mathúna DP, Gibson F, Shields L, Leclercq E, Sheaf G. *Interventions for promoting participation in shared decision-making for children with cancer*. Cochrane Database of Systematic Reviews 2016.

development, adolescents are viewed to be equally as cognitively developed. As noted by Piaget, at this age, “intelligence is demonstrated through the logical use of symbols to abstract concepts” such as those of their rights. It has been shown that, from the ages of 14 and above, adolescents have a marked change in the ability to understand their rights and personal autonomy through self-determination.<sup>246</sup> Within this age group, adolescences are able to demonstrate a level of competency equivalent to that of adults based on four standards of competency (evidence of choice, reasonable outcome, rational reasons, and understanding).<sup>247</sup>

Prior to this age, children see rights as “arbitrarily granted by adults,” while as they grow older, they comprehend the concept through a lens of social order.<sup>248</sup> However, it is important to note that “children as young as nine” are still able to provide preference in their treatment options, despite not fully considering critical components of risks disclosed to them. Thus, both the assent and dissent of pre-adolescent children must be considered when considering the administration of vaccines. Children within this age group should be involved in decision-making processes regarding their health, but not provided a fully autonomous role in decision-making.<sup>249</sup>

Generally, decision-making regarding the health care of young patients is a shared responsibility between the physician and the parents or guardians. Thus, parents must provide consent (with the elements of standard informed) consent prior to the administration of medical treatments.<sup>250</sup> Particularly, with children, informed consent becomes difficult to attain because it is often given through a proxy – their parents or guardians. Where a minor does not have the capacity to consent to an intervention, the intervention may only be carried out with the authorization of his or her representatives or an authority or a person or body provided for by law.

Investigators should understand the evolvement of parental intent processes. This surrogate decision-maker generally acts in the “best interests of the child”, but this principle has proven to be difficult to define. Investigators should understand the evolvement of parental intent processes. Sufficient information should be given to parents to determine if to agree their children to participate in the clinical trials. Cultural values regarding child-rearing play a large

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<sup>246</sup> Bruzzese JM, Fisher CB. Assessing and enhancing the research consent capacity of children and youth. *Applied Developmental Science*. 2003 Jan 1;7(1):13-26.

<sup>247</sup> Weithorn LA, Campbell SB. The competency of children and adolescents to make informed treatment decisions. *Child development*. 1982 Dec 1:1589-98.

<sup>248</sup> Bruzzese JM, Fisher CB. Assessing and enhancing the research consent capacity of children and youth. *Applied Developmental Science*. 2003 Jan 1;7(1):13-26.

<sup>249</sup> Weithorn LA, Campbell SB. The competency of children and adolescents to make informed treatment decisions. *Child development*. 1982 Dec 1:1589-98.

<sup>250</sup> Studies have shown that parents are less likely to have their children vaccinated if the majority of the other children are vaccinated. For instance, as mentioned by O’Neill, in the United Kingdom, parents were been given the right to refuse to have their children vaccinated. The proportion of children vaccines with measles, mumps, and rubella (MMR) has fallen, so that free-riders now face a problem.

role in these decisions.<sup>251</sup> This creates an ethical dilemma, as those providing consent are often thinking foremost in their roles as caregivers, and not in the child's best interest.

Children should not be treated as completely mature rational decision-makers but should participate in the decision-making process.<sup>252</sup> Information should be provided to pre-adolescent and adolescent children in an age-appropriate manner, which takes into consideration their health literacy.<sup>253</sup> Basing voluntariness on the development of the individual children means that this group should be able to make decisions within their capacity; otherwise a legal surrogate should make the decision.<sup>254</sup> The law demands a child who has 'sufficient understanding and intelligence to understand what is proposed' to give consent.<sup>255</sup>

Investigators should recruit young children by supplying them with information opportune to their level of comprehension.

### 7.2.2. Women/Gender

Gender has been shown to impact the quality of healthcare.<sup>256</sup> Effort to define if women take part at the clinical studies to the same extent as men, and whether women have been underprivileged by systems and practices regarding their participation should be analyzed. Physicians must critically consider the ways in which gender may impact their relationship with patients, in order to avoid reinforcing gendered bias. Particularly, physicians must be cognizant of the ways in which their decision-making authority acts as a power structure within the construction of gender. Gender and power relations create an asymmetrical relationship, whereby the physician is the "holder of knowledge, authority, activity and dominance" and the female patient is a passive participant.<sup>257</sup>

Furthermore, gender plays a role in the variation of communication style between individuals.<sup>258</sup> These differences in communication style impact patient communication, as studies have shown that patient-behavior reciprocates gender-linked physician behavior.<sup>259</sup>

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<sup>251</sup> Committee on Bioethics. Informed consent, parental permission, and assent in pediatric practice. *Pediatrics*. 1995 Feb 1;95(2):314-7.

<sup>252</sup> Committee on Bioethics. Informed consent, parental permission, and assent in pediatric practice. *Pediatrics*. 1995 Feb 1;95(2):314-7.

<sup>253</sup> Caldwell PH, Murphy SB, Butow PN, Craig JC. Clinical trials in children. *The Lancet*. 2004 Sep 3;364(9436):803-11.

<sup>254</sup> Weithorn LA, Campbell SB. The competency of children and adolescents to make informed treatment decisions. *Child development*. 1982 Dec 1;1589-98.

<sup>255</sup> *Gillick v West Norfolk and Wisbech Area Health Authority and Department of Health and Social Security* [1984]

<sup>256</sup> Ellingson LL, Buzzanell PM. Listening to women's narratives of breast cancer treatment: A feminist approach to patient satisfaction with physician-patient communication. *Health Communication*. 1999 Apr 1;11(2):153-83.

<sup>257</sup> Ellingson LL, Buzzanell PM. Listening to women's narratives of breast cancer treatment: A feminist approach to patient satisfaction with physician-patient communication. *Health Communication*. 1999 Apr 1;11(2):153-83.

<sup>258</sup> Roter DL, Hall JA. Physician gender and patient-centered communication: a critical review of empirical research. *Annu. Rev. Public Health*. 2004 Apr 21;25:497-519.

<sup>259</sup> Roter DL, Hall JA. Physician gender and patient-centered communication: a critical review of empirical research. *Annu. Rev. Public Health*. 2004 Apr 21;25:497-519.

Studies in feminist critical thought have noted that women often perceive things through an emotional 'lens', which in turn makes them more vulnerable as a patient and thus would require additional protections.<sup>260</sup> Additionally, gender concordance results in more lengthy visits and equal contributions from both parties regarding medical dialogue.<sup>261</sup>

About informed consent, as FISABIO assert: "Tam et al. didn't find significant differences to understanding informed consent in clinical trial by gender, only few studies point to differences and in most cases reflect and advantage in understanding, or even in the frequency to read the entire ICF, by women. Even so, is important to consider that we didn't find studies that analyze the gender differences in comprehension with ICF adapted to gender. The effect of how accommodation and adaptation by gender can affect understanding of the IC, especially by women, or the impact it may have on decision-making about participation in research, has never been studied and we think is a field that should be considered. Accommodation may also make IC form or process more attractive and increase the proportion of people who read the whole IC."<sup>262</sup>

Lastly, gender also plays a role within the context of culture and family relationships. In some communities, women may express their wishes to have a male relative's permission prior to providing consent for treatment.<sup>263</sup>

### 7.2.3. Pregnant Women

Recent studies have emerged globally on the recruitment of pregnant women into clinical research trials (CRTs) exploring a variety of biomedical and social issues specific to this population.<sup>264</sup>

Ethical issues arise in clinical research that involves pregnant women as participants.<sup>265</sup> Specifically, ethical issues arise as a consequence of the interdependence between the health of the mother and the fetus. Generally, a pregnant woman is able to protect her own interest. However, a pregnant woman is responsible for protecting not only her own interests, but also

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<sup>260</sup> Montini T. Gender and emotion in the advocacy for breast cancer informed consent legislation. *Gender & Society*. 1996 Feb;10(1):9-23.

<sup>261</sup> Roter DL, Hall JA. Physician gender and patient-centered communication: a critical review of empirical research. *Annu. Rev. Public Health*. 2004 Apr 21;25:497-519.

<sup>262</sup> Fisabio: About gender differences A.9.3 with ICTs, p. 74.

<sup>263</sup> Halkoaho A, Pietilä AM, Ebbesen M, Karki S, Kangasniemi M. Cultural aspects related to informed consent in health research: a systematic review. *Nursing ethics*. 2016 Sep;23(6):698-712.

<sup>264</sup> Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton JA. *Enrolling pregnant women: issues in clinical research, Womens Health Issues*, 2013, v 23.

<sup>265</sup> Lyerly AD, Little MO, Faden R. The second wave: Toward responsible inclusion of pregnant women in research. *IJFAB: International Journal of Feminist Approaches to Bioethics*. 2008 Sep;1(2):5-22.

those of her fetus, which is unable to provide consent.<sup>266</sup> <sup>267</sup> A fetus may have unique considerations to risks and other health-related issues to be considered by the mother when providing consent. One such consideration is the vaccination's ability to protect (and be safe) for both the mother and fetus because of the antibody transfers by the placenta.<sup>268</sup> The mother's decision to protect herself from an infectious disease through vaccination may also pose therapeutic benefits and risks to the fetus.<sup>269</sup> Thus, communications with a pregnant woman is of incredible importance as any perceived benefits or risks to either her or the fetus may play an important role on decision-making.<sup>270</sup>

### 7.3 Principles of Informed Consent in the Context of Three Vaccination Case Studies: Meningitis, RSV, and HPV Vaccines

Both unvaccinated and inadequately vaccinated individuals can pose a serious risk to others within their communities, due to the potential for transmission (in the community) of infectious diseases. In using vaccines against meningitis, RSV, or HPV—like with all vaccines—the implementation of ethical principles should be balanced with promotion of adequate vaccination. The ethical challenges in the specific context of meningitis, RSV, or HPV vaccination arise from the fact that the main target group for immunization includes vulnerable persons: namely, infants, preadolescents, adolescents, and pregnant women. Clinicians and researchers will therefore inevitably face challenges in satisfying the requirements of traditional fully informed consent norms among this target group.

Specifically, to satisfy the requirements of an ethically valid informed consent, each member of this group—including parents as proxies for infants, preadolescents, and adolescents—must be given the opportunity to not only ask questions pertaining to the vaccination, but to also receive appropriate answers to such questions. These following considerations must be disclosed to the vulnerable groups identified: (1) the condition for which the vaccination is proposed; (2) the nature (i.e. regimens, doses, and schedules) of the proposed interventions; (3) the risks and benefits that a “reasonable person” would expect to be told about; and (4) alternative courses of infection prevention.<sup>271</sup> Collectively, these considerations thus require that clinicians and

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<sup>266</sup> Grisso T, Appelbaum PS. Assessing competence to consent to treatment: A guide for physicians and other health professionals. Oxford University Press, USA; 1998.

<sup>267</sup> Rasmussen SA, Watson AK, Kennedy ED, Broder KR, Jamieson DJ. Vaccines and pregnancy: past, present, and future. In: Seminars in Fetal and Neonatal Medicine 2014 Jun 30 (Vol. 19, No. 3, pp. 161-169). WB Saunders.

<sup>268</sup> Rasmussen SA, Watson AK, Kennedy ED, Broder KR, Jamieson DJ. Vaccines and pregnancy: past, present, and future. In: Seminars in Fetal and Neonatal Medicine 2014 Jun 30 (Vol. 19, No. 3, pp. 161-169). WB Saunders.

<sup>269</sup> Grisso T, Appelbaum PS. Assessing competence to consent to treatment: A guide for physicians and other health professionals. Oxford University Press, USA; 1998.

<sup>270</sup> Chambers CD, Polifka JE, Friedman JM. Drug safety in pregnant women and their babies: ignorance not bliss. *Clinical Pharmacology & Therapeutics*. 2008 Jan 1;83(1):181-3.

<sup>271</sup> Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical?. *Jama*. 2000 May 24;283(20):2701-11.



researchers disclose *all* information that a reasonable patient or participant would require in order to reach an informed decision about vaccine administration or research.<sup>272</sup>

The idea of a “reasonable person”, as alluded to in Canadian case law, needs to take into account that the patient or research participant, especially one that is vulnerable and marginalized in society: (1) is not an expert in the medical field or the study; and (2) relies on the clinician’s or researcher’s “special skill, knowledge and experience”, which puts the clinician/researcher in a fiduciary position.<sup>273 274</sup> This fiduciary position arises from a duty to ensure, at all times, the right of the individual to the safeguard of their integrity, which is an ethical obligation arising from the World Medical Association’s Declaration of Helsinki.<sup>275</sup>

### 7.3.1 Consent Barriers: HPV Vaccination

There have been focused efforts through research to identify consent barriers to HPV vaccination; certain elements of which we propose are highly transferable to the meningitis and RSV vaccinations.

To this end, a study examining HPV vaccine promotion in the African-American community has identified the following key factors affecting HPV immunization among African-American mothers and their adolescent daughters:<sup>276</sup>

- Experience: The mothers’ experience of cervical dysplasia and cervical cancer (CD/CC)<sup>277</sup> motivated a strong commitment to protect their daughters from the trauma of CD/CC;
- Comprehension: Limited understanding of HPV and its connection to CD/CC among the mothers made it difficult for them to evaluate the risk of infection or to explain the medical benefits of the vaccine to their daughters;
- Advocacy/Endorsement: The mothers’ anticipation of their adolescent daughters’ sexual activity, leading the mothers to advocate for health care interventions to protect their daughters; and
- Trust: The mothers’ trust in their physicians to initiate discussion of HPV immunization.

This study also revealed that mothers trusted physicians to initiate discussion of HPV vaccination. Physicians who failed to initiate discussion with the mothers—and thereby failed

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<sup>272</sup> The patient must understand the information disclosed, and a voluntary decision must be made based on the information presented.

<sup>273</sup> Halushka v University of Saskatchewan. Sask CA. 1965. p. 444.

<sup>274</sup> Weiss v Solomon. QC CS. 1989. p. 741-742.

<sup>275</sup> Assembly WG. WMA Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects. World Medical Association, Somerset West, South Africa. 1996.

<sup>276</sup> Hamlish T, Clarke L, Alexander KA. Barriers to HPV immunization for African American adolescent females. Vaccine. 2012 Oct 5;30(45):6472-6.

<sup>277</sup> HPV infection is sexually transmitted and can cause cervical dysplasia (CD) and cervical cancer (CC). Having multiple sexual partners increases exposure to HPV, and intercourse at an early age exposes the cervix to HPV when it is most vulnerable to infection. Alguire PC. Internal medicine essentials for clerkship students 2. ACP Press; 2009.

to seek informed consent for vaccination—generated doubt about the vaccine among mothers, and consequently, missed opportunities for immunization among the adolescent women.

Additionally, a mix of perceived barriers to HPV vaccination have been identified in a separate study by Florida State University. This investigation concluded that perceived barriers to behavior change are influential determinants of health behavior (such as a women’s intentions to receive the HPV vaccine). Specifically, vaccine cost, pain, safety, side effects, perceived appropriateness to one’s lifestyle (e.g. not being sexually active), and need for multiple doses, were identified as the key barriers at play for HPV vaccination.<sup>278</sup> These multidimensional barriers are equally relevant to our present investigation into HPV, meningitis, and RSV vaccination, as they may affect our vulnerable target groups’ intentions to get vaccinated for the three infectious diseases.

### 7.3.2 Consent Barriers: HPV, Meningitis, and RSV Vaccination

This report proposes that the various consent barriers to HPV vaccination outlined in the previous section may be expanded and modified to encompass the cases of meningitis and RSV vaccination involving vulnerable groups, especially young people and pregnant women. In expanding its application to all three vaccination cases, this report proposes recommendations to mitigate the perceived barriers to vaccination among our target group of vulnerable individuals.

To ensure culturally relevant vaccine promotion among our target group of children, adolescents, and pregnant women in the context of meningitis and RSV vaccination administration or research, previous research outcomes pertaining to HPV vaccination among vulnerable groups must be expanded. Specifically, physicians and researchers should identify and resolve (or avoid) immunization consent barriers relating to: experience; comprehension; advocacy/endorsement; and trust.

Additionally, HPV, meningitis, and RSV vaccination administration or research could benefit from a tailored consent process that carefully considers influential behavioral barriers to initiating vaccination among our vulnerable target group. The attitudes and beliefs about vaccine acceptability were previously investigated in the context of young adult women’s perceived barriers to initiating HPV vaccination;<sup>279</sup> therefore, it is only reasonable to expand the ambit of the following behavioral barriers to meningitis and RSV vaccination: namely, vaccine cost, pain, safety, side effects, perceived appropriateness to one’s lifestyle (e.g. sexual abstinence) and need for multiple doses.

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<sup>278</sup> Gerend MA, Shepherd MA, Shepherd JE. The multidimensional nature of perceived barriers: Global versus practical barriers to HPV vaccination. *Health Psychology*. 2013 Apr;32(4):361.

<sup>279</sup> Gerend MA, Shepherd MA, Shepherd JE. The multidimensional nature of perceived barriers: Global versus practical barriers to HPV vaccination. *Health Psychology*. 2013 Apr;32(4):361.

## 7.4. Recommendations

In addition to the specific recommendations suggested in the course of the report related to issues of multiculturalism, interreligious dialogue and neurobioethics, in this last chapter the trajectory of the research will build on the previous chapters and attention will instead be directed towards the more specific objective relevant to the I-Consent project, namely that of vaccination.

These recommendations highlight the priority needs that should be addressed in the context of informed consent for the administration of vaccines and for the translational/clinical vaccine research in general with specific emphasis on vaccination cases involving young people and pregnant women.

By way of improving the readability and design of consent forms for participation in clinical trials of vaccines, along with implementing innovative educational strategies such as “teach-to-goal”,<sup>280</sup> the informed consent form should be easy to be comprehensible, overall highly to clarify the contents (the purpose of the study, the procedures performed during the trial, extent of record confidentiality, compensation, and alternative treatments available), the potential harms and benefits, the involvements of the use of a placebo or other, the care that will be afforded, and the potential indemnity arising from the trial has been shown to be achievable with vulnerable, diverse populations—especially among those with literacy or language barriers, and those with minority status.<sup>281 282</sup>

We now turn to recommendations to address specific immunization consent barriers presented by the following vulnerability traits, which are unique among our target group of children, adolescents, and pregnant women: cognitive or communicative; social; and legal vulnerabilities.

With regard to accommodating cognitive or communicative needs among our target group, we propose:

- drafting consent forms in lay language; or
- discussing the consent in-person; and
- inviting a follow-up with the individual to answer questions at every step of the consent process;

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<sup>280</sup> For example, a strategy in which participants must respond correctly to a series of comprehension questions in order to participate in research or clinical interventions.

<sup>281</sup> Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton JA. Enrolling pregnant women: issues in clinical research. *Women's Health Issues*. 2013 Feb 28;23(1):e39-45.

<sup>282</sup> Gazzinelli MF, Souza VD, Araújo LH, Costa RD, Soares AN, Maia CP. Theater in the education of children and teenagers participating in a clinical trial. *Revista de Saúde Pública*. 2012 Dec;46(6):999-1006.

- additional recommendations relating to the consent barrier of comprehension, as detailed in Table 2, below.

As for addressing the social vulnerability barriers to consent among children, adolescents, and pregnant women, a critical point in addressing discrimination based on age and gender is acknowledgement of its existence. Physicians and researchers must be able to recognize the kind of issues or situations where an individual among our target group may be prone to feel discriminated against in the context of vaccination administration or research: for example, cases where a pregnant woman (or young person) may be inadequately informed in the consent process, owing to a physician's or researcher's prejudicial attitudes against women (or prejudicial presumptions that an individual under their care is not able to comprehend the information due to young age). In order to successfully address social vulnerability among our target group of vulnerable individuals, physicians and researchers must also be held accountable in cases of blatant discrimination.

Legal vulnerability barriers to consent—especially among infants, preadolescents, and adolescents who are unable to legally consent —can be addressed by obtaining consent from a legal representative (such as a parent as proxy for the child). For pregnant women or parents that are concerned about their consent creating potential legal repercussions for themselves or their children,<sup>283</sup> researchers should take steps to legally protect the patients and participants under their care. Unlike doctors (or lawyers), researchers do not have the legal privilege of confidentiality with their study participants. In view of that obstacle, to help protect the privacy of young individuals and pregnant women enrolled in sensitive vaccine-related research, this report recommends governments enact laws allowing researchers to obtain exceptional privileges akin to policies on the granting of Certificates of Confidentiality (CoCs). CoCs, which are issued by research facilities and agencies of the U.S.'s Department of Health and Human Services (HHS), permit researchers to refuse to disclose identifying information about their participants when subpoenaed by a court of law.<sup>284</sup>

As for additional recommendations, the report hopes to identify and resolve (or avoid) immunization consent barriers relating to experience, comprehension, advocacy/endorsement, and trust, as detailed in Table 2 below. This would be *before* an individual belonging to the report's vulnerable groups decides on consenting to the vaccine administration or research.<sup>285</sup> In so doing, the respect of the individual's autonomy, dignity, and privacy with respect to their body and their personal health information will be entirely satisfied

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<sup>283</sup> E.g. their or their children's vulnerability to genetic discrimination based on "genetic predisposition or carrier status".

<sup>284</sup> Welcome to Certificate of Confidentiality Homepage | Research Involving Human Subjects [Internet]. Humansubjects.nih.gov. 2017 [cited 5 March 2018]. Available from: <https://humansubjects.nih.gov/coc/index>

<sup>285</sup> For instance, project or vaccination objectives; identity of researchers/clinicians; anticipated outcomes; and potential risks and benefits, among other information.

by physicians and researchers, strengthening meningitis, HPV, and RSV vaccination programs to the benefit of our vulnerable target group.

Consent Barrier	Recommendations
<ul style="list-style-type: none"> <li>● Experience</li> </ul>	<p>Acknowledge a young person's or pregnant woman's meningitis, CD/CC, or RSV experience(s), to help establish appropriate rapport with the target group. In so doing, the approach is two-fold:</p> <ul style="list-style-type: none"> <li>● on the one hand, the vulnerable individual's concerns, working with the presumption that the individual may have no (or minimal) prior contact or appreciation with the use of vaccination in clinical research (or with preventive medical care through vaccination administration), and may be somewhat apprehensive of participating must be addressed;</li> <li>● on the other hand, providing the individual with adequate information to ensure that they understand this information (which ties into our discussion on the consent barrier relating to comprehension, below) is also integral.</li> </ul>
<ul style="list-style-type: none"> <li>● Comprehension</li> </ul>	<p>Provide a consent procedure that facilitates an understanding of meningitis, HPV, and RSV; and the connection between untreated infections, CD/CC, and poor hand hygiene, respectively. This may be accomplished by either:</p> <ul style="list-style-type: none"> <li>● writing consent forms in lay language; or</li> <li>● discussing the consent in-person; and</li> <li>● inviting a follow-up with the individual to answer questions at every step of the consent process.</li> </ul> <p>If working with patients or participants where capacity to consent is an issue (such as a young child, or a pregnant woman limited by a mental defect or disorder), it may be necessary to:</p> <ul style="list-style-type: none"> <li>● include a procedure to assess the individual's capacity to consent; and</li> <li>● if capacity is deemed not to exist, obtain consent from a surrogate or proxy who is legally responsible for the individual.<sup>286</sup></li> </ul>
<ul style="list-style-type: none"> <li>● Advocacy/Endorsement</li> </ul>	<p>Support parenting strategies and lifestyle practices that reduce and reverse the risk factors that predispose the target group to infection. Such risk factors include:</p>

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<sup>286</sup> It should be noted that, although the individual may not be able to process the full meaning of consent, it is still important to involve the individual in the consent procedure to the extent of their capability.

	<ul style="list-style-type: none"> <li>● untreated infections, for meningitis;<sup>287</sup></li> <li>● sexual activity, for CD/CC; and</li> <li>● failure to wash hands, especially before touching one's baby, for RSV.</li> </ul>
● Trust	<p>Ensure trust, and thereby cooperation, with the target group, by:</p> <ul style="list-style-type: none"> <li>● initiating discussion of meningitis, HPV, or RSV immunization; and</li> <li>● clearly explaining the connection between prevention of the infection and its respective immunization.</li> </ul>

Table 2: Consent Barriers and Recommendations, in the context of Meningitis, HPV, and RSV Vaccination Administration or Research involving Children, Adolescents, and Pregnant Women

The final section of the report will discuss the influential behavioral barriers in initiating meningitis, HPV, and RSV vaccination programs among young people and pregnant women: specifically, concerns relating to vaccine cost, pain, safety, side effects, perceived appropriateness to lifestyle, and need for multiple doses. In terms of recommendation, the interventions adopting an individualized approach to promoting health protective behaviors may be particularly effective in resolving (or avoiding) multidimensional consent barriers to vaccination.<sup>288</sup> For example, if a woman were to express general concerns about the safety or effectiveness of the meningitis, HPV, or RSV vaccine, the consent process could be tailored (via integration of intervention materials, such as tailored educational materials) to focus on reducing her concern. If, on the other hand, more practical concerns were raised regarding time constraints or the inability to pay for the vaccine, interventions should be aimed at helping the woman find a convenient time to receive the vaccine or directing her to clinics or other institutions that offer the vaccine at a reduced rate.

With a particular focus on consent practices applied to vaccination research (where ethical challenges abound in obtaining informed consent), this report recommends that a dynamic informed consent model with participant control is most effective. On the individual level, it is conceivable for researchers to keep the vulnerable target group informed of how their personal health information is being used in *current* ongoing research, via platforms such as regular

<sup>287</sup> For example, meningococcal disease is a rare but serious and potentially fatal disease that is vaccine preventable. Of particular note is that infants and children under 5 years of age, along with teens and adults between 15 to 24 years of age, are at highest risk. While meningococcal disease and its complications, such as meningitis, are uncommon, the consequences can be devastating - ranging from hearing loss, memory difficulty, learning disabilities, and brain damage, to gait problems, seizures, kidney failure, shock, and death.

<sup>288</sup> "Perceived Barriers To Self-Management And Preventive Behaviors - Behavioral Research Program". *Cancercontrol.cancer.gov*. Web. 14 Mar. 2018.

newsletters (in print or digital formats), and/or interactive websites.<sup>289 290 291</sup> In this regard, given appropriate privacy safeguards, pregnant women, adolescents, and parents as proxies for their children could be provided individual online accounts, which they could access to: *update* their health information and research preferences; *review* the details of the research projects in which their tissue samples and data are being used; and *opt out* if desired. This mechanism can equally be used to seek new tissue samples and data from our target group, for *future* research projects.

As for practical applications of dynamic consent mechanisms, there has been a shift in the U.S. toward allowing more control by participants and patients with regards to how the data pertaining to them is used in research. Indeed, some groups in the U.S. have developed tools that allow research participants to exert more control over data use. A case in point is Sage Bionetworks, a non-profit organization based in Seattle, which has developed and maintains an open-source software called the “Participant Centric Consent (PCC) toolkit”.<sup>292</sup> The PCC toolkit facilitates the implementation, by researchers or healthcare workers, of a participant-centered consent process into the design of their research projects. More accurately, the PCC toolkit promotes both data sharing and participant/patient engagement in research, by providing an interactive “e-consent” approach that engages and informs prospective study participants about research projects they may join. The toolkit has been implemented by five clinical research studies that are currently ongoing in the U.S (i.e. at Sage Bionetworks, Stanford University, Icahn School of Medicine at Mount Sinai, and Massachusetts General Hospital).<sup>293</sup>  
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In its capacity as an ongoing, dynamic informed consent mechanism with participant control, this approach to consent in vaccine research would honor the spirit of informed consent. By ensuring that vulnerable subjects have access to relevant information as it arises (regarding their participation in both *current* and *future* research), researchers are able to keep the initial consent alive throughout the duration of their research. Likewise, from the informational point of view, potential participants to vaccine research studies are equally informed of who is the data custodian (e.g. the research institution), what technical methods (e.g. anonymization)

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<sup>289</sup> Petrini C. “‘Broad consent’, exceptions to consent and the question of using biological samples for research purposes different from the initial collection purpose. *Social Science & Medicine*. 2010 Jan 31;70(2):217-20.

<sup>290</sup> Kaye J, Whitley EA, Lund D, Morrison M, Teare H, Melham K. Dynamic consent: a patient interface for twenty-first century research networks. *European Journal of Human Genetics*. 2015 Feb 1;23(2):141-6.

<sup>291</sup> Caulfield T, Knoppers BM. *Genome Canada. Consent, Privacy & Research Biobanks* 2010. p. 4.

<sup>292</sup> Angrist M. Start me up: ways to encourage sharing of genomic information with research participants. *Nature Reviews. Genetics*. 2015 Aug 1;16(8):435.

<sup>293</sup> mPower mobile Parkinson Disease Study [Internet]. [Parkinsonmpower.org](http://parkinsonmpower.org). 2017 [cited 5 March 2018]. Available from: <http://parkinsonmpower.org/>

<sup>294</sup> MyHeart Counts | Stanford Medicine [Internet]. [Med.stanford.edu](http://med.stanford.edu). 2017 [cited 5 March 2018]. Available from: <https://med.stanford.edu/myheartcounts.html>

<sup>295</sup> Asthma Health App | Apple ResearchKit | Icahn School of Medicine at Mount Sinai [Internet]. *Asthma Health App | Apple ResearchKit*. 2017 [cited 5 March 2018]. Available from: <http://apps.icahn.mssm.edu/asthma/>

<sup>296</sup> GlucoSuccess [Internet]. [GlucoSuccess.org](http://glucosuccess.org). 2017 [cited 5 March 2018]. Available from: <http://glucosuccess.org/index.html>



have been adopted by the institution to protect their confidentiality, who will have access to the data, and how to withdraw their consent, if desired. Indeed, by implementing a participant-centered informed consent model to vaccine research involving children, adolescents, and pregnant women, researchers will convey all the necessary information in order to allow the participants involved to decide if they want to assume the risks derived from their participation (including potential associated risks from the use of their personal information).<sup>297</sup> As such, dynamic informed consent with participant control would be a most appropriate consent model to promote our vulnerable target group's right to autonomy in current and prospective vaccine research.

## Table of results

### Conclusions from a neurobioethical perspective

#### *Recommendations to increase the researcher grasp of patient competence:*

- Implementing technological advancements in our understanding of the brain so to provide a more fixed way to classify competence.
- Appropriately re-considering the importance of adopting an effective patient-centered approach (promoting a holistic approach to patient care), which reveals its urgent necessity and appropriateness, especially (although not only) with regard to a physician-patient relationship involving foreign patients or research participants.

#### *Recommendations to implement recent discoveries in neurobioethics:*

- Changing the categorization of the patients focusing on a specific version of autonomy (patient-centered) as not as absolute as sometimes given.
- Taking into account claims for new specificities of some human rights, as cognitive liberty, mental privacy, mental integrity and psychological continuity due to the fact that cognitive and other type of enhancers might paradoxically create new groups of vulnerable populations (e.g. soldiers).

### Conclusions from multiculturalism and interreligious perspective

#### *Recommendations to increase the effectiveness of multicultural and interreligious perspective:*

- Taking into account that not all traditions and religions give the same level of importance to the individual-centered version of autonomy at the base of informed consent form conceived to be signed by a single individual.

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<sup>297</sup> Cavoukian A, Castro D. Big Data and innovation, setting the record straight: De-identification does Work. White Paper, Jun. 2014 Jun 16.

- Implementing some key terms directly referring to some cultural and religious traditions. Considering other key notions such as human duties, not only human rights.
- Fostering participation of trained cross-cultural professionals as members of the ethical research committees to validate cultural and religious concerns during research. Increasing the diversity of the health care professionals, improve the opportunity to have individuals capable to filter more directly certain scientific notions into some religious and traditional guidelines.
- Stimulating the composition of cross-cultural research teams, facilitating understanding of cultural and religious diversity when recruiting and when carrying out research in patients with different cultural backgrounds and religious convictions.
- Capturing the patient religious or cultural background to allow the researcher to introduce appropriate religious and cultural concepts (or terms), when necessary, in the IC form and during the communication process, facilitating the understanding, trust and acceptance of believers towards social value of science and research, improving the acceptance rate of participation in clinical trial.
- Changing the categorization of the patients focusing on a shared common cultural identity. Health care professionals should ask questions about other social identities to shift their attention from the patient's ethnicity or religious background helping to reduce racial or cultural biases to improve recruitment of minorities.
- Fostering the religious and community leaders' analysis and possible support or approval of specific scientific biomedical researches (i.e. specific therapy or vaccines) so that their support might illuminate believers and increase the trust towards doctors and researchers as well as participation in clinical trials.

## Conclusions on the investigator bias in the informed consent obtaining process and recommendations to reduce it

### *Recommendations to reduce the optimism bias by:*

- Presenting (investigators) real survival data during the process of informed consent from previous patients that have participated in the same trial, so both the patient and the researcher become aware of the reality and reduce the optimism bias of obtaining a high medical benefit.

### *Recommendations to reduce the effects of implicit bias by:*

- Increasing the diversity of the health care professionals, help to reduce racial biases and improve recruitment of minorities.
- Changing the categorization of the patients focusing on a shared common identity. Health care professionals should ask questions about other social identities to shift their attention from the patient's ethnicity.
- Taking (investigator) the perspective of the other side has shown to improve empathy.

- Fostering self-affirmation in order to improve the patient-researcher relationship and decrease racial issues by affirming self-integrity values.

### Conclusions on the understanding and readability of informed consent

- Specific and technical terms such as placebo or randomization are not normally comprehended by the patients.
- Length of the informed consent is inversely proportional to patient understanding.

#### *Strategies to improve understanding by:*

- Enhancing consent forms with better design, text styling, readability improved, summary sections, added pictures, shorter sentences, etc.
- Fostering extended discussion with research staff.
- Using multimedia resources such as videos, computer presentations and PowerPoint slides with audio narration, etc.

### Conclusions on privacy

#### *Strategies to protect privacy interests and promote research by:*

- Offering to participants regular notifications of results and updates regarding the clinical trial.
- Promoting patient participation at a more institutional level by involving patient associations and applying and developing policies.
- Submitting to an Institutional Review Board (IRB) in those cases where investigators request access to medical information not collected for research purposes, to determine if the criteria for waiving consent is met. In these cases, the investigator will need to demonstrate the need of those data to conduct the research, the minimum risk for the subject's privacy, and the maximum protection of patient's privacy by using identifier codes and the use of the minimum information required.
- Asking hospitals and other institutions active in research to inform patients that their medical records may be used to identify them as potential subjects for clinical trials, being possibly contacted, but with a written opt out possibility.
- Including a committee with patient representatives who can address public concerns, that oversees the organizations that collect and stores the confidential health information.
- Wording of the informed consent considering the fact of continued use of information from participants, even after they withdraw from the procedures.
- Including in the consent form a statement affirming that confidential identifiable information may be held, in studies where a long-term follow up is anticipated known, it should be
- Including privacy and security safeguards to all parties that hold the identifiable health information such as internet service providers, website, device developers, mobile application, etc.
- Using data sharing protections, beyond the legal requirements, such as encryption, virtual private networks, tests for network threats, etc. Actually, there are methods

where you can allow access to a secondary user to analyze data without downloading it.

- Using technical approaches that aggregates the information and alters some values in a data set so that the data set is still useful for group analysis, but individual privacy reidentification is better protected.

## Conclusions on vulnerable groups

### *Recommendations to ensure the respect of vulnerable people by:*

- Making the consent forms easily readable and as clear as possible by ensuring the presence of statements on the agreement to participate, indication of the length of time an activity is likely to take, indication of what will happen to the information collected.
- Improving comprehension of the research by writing forms in lay language, discussing the content in-person and inviting a follow-up with the individual to answer questions at every step of the process.
- Fostering trust and cooperation of subjects of experimentation by explaining the connection between prevention of infection and its respective immunization in vaccine research.

### *Recommendations to reduce the risks for children and young people by:*

- Assuring actual capacity of properly processing information and sufficient understanding of what research involves, i.e. using friendly tools to illustrate the nature and interventions during the research process; assuring research personnel trained in dealing with this category of subjects of experimentation (according to age, culture, etc.).
- Making an assessment in order to exclude any possible coercion of children's participation through a screening of parental/societal context.
- Reporting any possible disclosure by a child of information that raises child protection concerns (e.g. information indicating that they are currently at risk of or are experiencing violence, exploitation or abuse) during the research process.

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