

# Informed consent: still a useful tool in research ethics

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## Abstract

This article discusses informed consent (IC): its evolution, its main challenges, and its theoretical assumptions. This process involves the interrelation of IC with the history and evolution of research ethics, and with some abuses committed in biomedical research. The article also presents the objections to IC, especially those related to its implementation in developing countries. It also approaches the epistemological problems and those related to the capacity of acting, given the background conditions in which IC is obtained. Furthermore, the article exposes the traditional justification of IC as conveyed by the Belmont Report, as well as a frequent simplification of this justification that focuses only on the deliberative aspect of IC, in which the emphasis on the autonomy or deliberation supposes an inadequate view of research subjects.

## Keywords

informed consent; assent form; the voluntary consent; free power of choice; autonomy; developing countries

## Introduction

Informed consent (IC) was one of the first resources of research ethics and, in a certain sense, it can be considered as emblematic. The history of research ethics is deeply related to IC. During the first period when research ethics issues began to be considered, it seemed that nearly all problems that abusive research presented could be solved if a good IC could be obtained.

The first cases to reveal the importance of IC in research ethics were the abuses during World War II.

Physicians forced people to drink seawater to find out how long a person could survive without fresh water. At Dachau, prisoners were immersed in icy waters to see how long a pilot might live when shot down over the English Channel and to find out what kinds of protective gear or rewarming techniques were most effective. Nazi military authorities were worried about diseases that the German troops could contract in Africa or Eastern Europe and physicians in the camps used the “human materials” at their disposal to develop remedies. Hundreds of people died in these experiments; many of those

who survived were forced to live with painful physical or psychological scars (Annas & Grodin 1992).

These experiments were perpetrated by Nazis during wartime. Germany at that time was scientifically highly advanced and these experiments were conducted by German physician-researchers (Annas & Grodin 1992).<sup>1</sup> They represent aberrations in the field of non-therapeutic research. One of the issues to be considered about these situations was that research subjects were prisoners of war in a condition of total subordination without any chance of consent (Luna 2007).

This kind of abuse led later to the writing of the Nuremberg Code. Even if it is not the first document in the area of research ethics, it is paradigmatic and one of the most well known documents. Its intention was to rule out unethical research and the focus was put on IC. In fact, the first article is concerned with IC, whose requirement is so high that only adults with legal capacity could consent. Its first article (1947) reads:

The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

This is, undoubtedly, a strong and clear article which states the importance of IC and establishes the main elements that should be present. However, the Nuremberg Code was not enough to stop abusive research later. Unfortunately, abuses in research were also done in times of peace and prosperity. These cases took place during the so-called “gilded age of research” in the United States. This was a time where life seemed to be improved by “progress” and where illnesses and diseases were going to be stopped by good science. There was a sort of faith in science and progress, and humanity seemed to be getting to an era of comfort and well-being. But not all was golden, and even at that time abusive cases were revealed. When these cases are analyzed, it can be understood why IC seemed to be the answer or at least a very important answer to prevent future cases alike.

An infamous case was the Tuskegee experiment, which lasted for 40 years, from 1932 to 1972. The experiment aimed to investigate the natural process of syphilis in black men of scarce resources in Alabama, the South

of the US. It was done by the US Public Health Service. The research subjects thought they were receiving treatment, but were actually being given some preparations. The study began at a moment when there was no good treatment to this illness, but it continued decades after when penicillin was discovered and this disease was effectively managed. In this case there was no IC. Research subjects were intentionally deceived.

The study about cancer immunity was another important case. In this experimentation, live cancer cells were injected into twenty-two human subjects. This was done in a period in which the word “cancer” was synonymous to death. According to a recent review, the subjects, who also found themselves in the condition of hospitalized patients, were “merely told they would be receiving ‘some cells’ – the word cancer was entirely omitted” (Rothman 1991: 74-5). Based on this case, one can see again how there are problems with IC. In this experiment, the researchers withheld important information about the study, jeopardizing the quality of the information to be provided in this process. An interesting point to outline regarding this case is that researchers had the correct “intuition”, and effectively cancer was not transmitted through the injections. In this sense, it can be said that research subjects were not “harmed” by the experiment. However, the deception involved in the process of IC and recruitment speaks of the wrongs that were done to the research participants.

Another case described in the literature also reveals problems with IC. In this case, artificial induction of hepatitis was carried out in an institution for children with mental problems in which a mild form of hepatitis was endemic (Rothman 1991). IC was asked to the parents of the children, but the only way to enter their children to this institution – a quite scarce resource at that time – was to accept them to be involved in this research. Again a “subtle coercion” was disrupting the process of IC.

All of these cases risked the lives and health of the individuals without their consent or approval (Rothman 1991).<sup>2</sup> Many of them were presented by anesthesiologist Henry Beecher (1966) in an article published in the *New England Journal of Medicine*. Unfortunately these cases do not represent only a few rare examples, but describe how mainstream investigators in the period between 1945 and 1965 exercised their broad discretion (Rothman 1991).<sup>3</sup> It concerned therapeutic research, isolated populations, or those with deficient education who were being misled. All of the cases presented express a characteristic problem of early bioethics: that of an inadequate respect for the autonomy of the research subjects. In this sense, the solution again was to enforce IC as a tool to avoid abusive research.

This article discusses informed consent (IC): its evolution, its main challenges, and its theoretical assumptions. This process involves the interrelation of IC with the history and evolution of research ethics, and with some abuses committed in biomedical research. The article also presents the objections to IC, especially those

related to its implementation in developing countries. It also approaches the epistemological problems and those related to the capacity of acting, given the background conditions in which IC is obtained. Furthermore, the article exposes the traditional justification of IC as conveyed by the Belmont Report, as well as a frequent simplification of this justification that focuses only on the deliberative aspect of IC, in which the emphasis on the autonomy or deliberation supposes an inadequate view of research subjects.

## The Helsinki Declaration and the Council for International Organizations of Medical Sciences/World Health Organization Guidelines

A question to consider is why the Nuremberg Code was not good enough and did not help avoiding the abusive cases during the gilded age of research. Part of the answer is that research in the gilded age was mainly therapeutic research and not only non-therapeutic as it was in war time. It also says that researchers felt the Nuremberg Code did not apply to them, for they were researchers, not “Nazis”. Finally, researchers also pointed to the fact that the requirement of IC in the Nuremberg Code was too strong and formalistic; the code was a document done by lawyers, and another kind of document was therefore necessary.

Because of these reasons, the Declaration of Helsinki arose as a document done by physicians for physicians. But note that, in the declaration, the place of IC changed and that there are other safeguards besides IC. For example, biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. It should also respect accepted scientific principles. Furthermore, the declaration points out that the responsibility for the human subject must always rest with a medically qualified person and never on the subject of the research, even though the subject has given his or her consent. IC articles appear in the last part of Section I of the Declaration of Helsinki, where basic principles are presented. Hence articles I. 9 and I. 10 say (World Medical Organization 1996):

I. 9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing.

I. 10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who isn't engaged in the investigation and who is completely independent of this official relationship.

Diverging from the Nuremberg Code, Helsinki allows research in persons without legal competence. Article I. 11 reads (World Medical Organization 1996):

I. 11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

In Section II, which deals with clinical research (medical research combined with professional care), the Declaration of Helsinki allows research without IC in certain cases (World Medical Organization 1996):

II. 5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1, 2).

Hence the Declaration of Helsinki was broader than the Nuremberg Code and allowed investigations that the code did not. It was focused not only on non-therapeutic research, but also on research that could benefit participants. The Declaration of Helsinki, therefore, stated the standard both of IC and of accepted procedures for an ethical research.

The International Ethical Guidelines for Biomedical Research Involving Human Subjects, also known as Guidelines of CIOMS (Council for International Organizations of Medical Sciences) and WHO (World Health Organization), were done in 1993, and their first intention was to complement the Declaration of Helsinki. In consequence, one can find in this document the same spirit of the declaration. For example, in its guideline 4, which speaks about individual informed consent, or in guideline 9, which covers the cases of special limitations on risk when research involves individuals who are not capable of giving informed consent, the same ideas of the Declaration of Helsinki and even some specifications more are presented.

It is also possible to find guidelines that complement Helsinki – for example, guideline 5, which details essential information that should be given to prospective research subjects: a) the reasons for considering the individual suitable for the research, and that participation is voluntary; b) that the individual is free to refuse to participate and will be free to withdraw from the research at any time without penalty or loss of benefits to which he or she would otherwise be entitled; c) the purpose of the research, the procedures to be carried out by the investigator and the subject, and an explanation of how the research differs from routine medical care; d) for controlled trials, a presentation of features of the research design (for instance, randomization, double-blinding), and the explanation that the subject will not be told of the assigned treatment until

the study has been completed and the blind has been broken; e) the expected duration of the individual's participation, including number and duration of visits to the research centre and the total time involved, and the possibility of early termination of the trial or of the individual's participation in it; f) any foreseeable risks, pain or discomfort, or inconvenience to the individual (or others) associated with participation in the research, including risks to the health or well-being of a subject's spouse or partner. The above mentioned are just six of the points that this guideline presents among other twenty other points.

In the CIOMS/WHO document there are also guidelines that are concerned with the obligations of sponsors and investigators regarding the adequate ways to obtain consent, such as guideline 6 or those covering vulnerable populations. For example, guideline 13 states that special justification is required for inviting vulnerable individuals to serve as research subjects and that, if they are selected, the means of protecting their rights and welfare must be strictly applied.

Regarding research involving children, guideline 14 specifies a set of conditions. It asks that before undertaking research with this group, the investigator must ensure that: the research might not equally well be carried out with adults; the purpose of the research is to obtain knowledge relevant to the health needs of children; a parent or legal representative of each child has given permission; the agreement (assent) of each child has been obtained to the extent of the child's capabilities; and that a child's refusal to participate or continue in the research will be respected. Hence, even if research in children is allowed, this document makes explicit safeguards that should be considered. In the same vein, guideline 15 is specifically devoted to research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent. It sets the conditions that should be accomplished in order to do research with this population.

Both documents, the Declaration of Helsinki and the CIOMS/WHO Guidelines, were revised subsequently, but changes were minor until 2000. Unfortunately the 2000 Declaration of Helsinki, together with its notes of clarification, and the 2002 CIOMS/WHO Guidelines will diverge in their last versions, but this is part of another story of research ethics (Luna 2007).

When analyzing the previous abusive cases, one finds that most of the problems they presented were related to an inadequate process of informed consent. As it can be inferred from the initial article of the Nuremberg Code to the CIOMS/WHO document, there has been an evolution and sophistication of this process, and IC was established as a necessary element of research. At this point of research ethics it seemed that nearly all the problems could be solved with a good IC: clear and precise information, no deception, no undue coercion. This all seemed to be the answer.

## Do developing countries pose special problems?

IC is a quite complex process. It is not just a form to be signed, even if many researchers do think about IC in this way. And even if it was established as a "golden rule" in research ethics, still nowadays IC faces many problems of implementation. For example, one issue is the great quantity of information it has to provide. Note that when guideline 5 of the CIOMS/WHO document was approached, just six points from the twenty six the guideline lists were mentioned. Even if it can be acknowledged the importance of giving each of these pieces of information to a possible research subject, it is very difficult to achieve this in a simple and understandable manner. Problems regarding the length of the forms of informed consent, the sophistication of some information to be provided, the capacity to understand, among others, are difficult to avoid, and are still a challenge for a good IC process.

Besides these general objections, several criticisms have recently appeared regarding IC in developing countries. They claim that IC is too formalistic, that it is insensitive to conditions, that it is too strict a requirement when risks are small, and that it is quite difficult to understand or to communicate the information. For example, one publication reporting on an international consultation says: "Too often informed consent is a one-way, one-time communication, a hurdle so that researchers can move on to the next stage of their research protocol" (Heise & Wood 2005: 19).

What are those conditions that may hamper IC in developing countries? The words read in articles about these countries are very similar: "[They are] socio-culturally diverse in terms of language, religion, economy and tradition. A great percentage of the population is highly vulnerable due to structural inequalities, racism, poverty, low literacy, and gender disparity" (BHAN et al. 2006: 39).<sup>4</sup>

The meaning of these words for many developing countries may be quite different. However, they can be correctly applied to Nigeria, Guatemala, Malawi or India, though the diversity, language, tradition or the religion may be remarkably distinct in each of them. Are there ways in which these differences may affect the informed-consent process?

It is now worth analyzing whether these criticisms are valid, whether IC in developing countries is a useless strategy. To do so, some strategies that could be followed in order to protect research subjects in a fitting manner will be presented. It is also important to point to two different aspects of IC: the first one has to do with epistemic conditions, that is, to the capacity of understanding information adequately; and the second aspect has to do with agency, freedom and the capacity of being truly voluntary. This last point is related to the background conditions in which IC is given. These background conditions may be limiting the capacity of action of individuals and are most likely to be present in situations of scarcity and extreme need, for example

in research settings often found in developing countries. The difference in nature of these two aspects of IC points to different kinds of problems. While the first of them may find relative good solutions, the second may prove to be more difficult to solve.

### Quality of IC in developing countries

A frequent assumption claims that the quality of IC in clinical research in developing countries is deficient, or worse than in developed countries. Part of the rationale has to do with the following quote: “Participants are illiterate, lack familiarity with biomedical research and IC, and have limited access to health care services” (Levine 1998; Resnik 1998; Alvarez Castillo 2002).

This is the assumption Christine Pace, Christine Grady and Ezequiel Emanuel considered in a preliminary paper.<sup>5</sup> In order to analyze whether the hypothesis is true, they compared data coming from developed countries and developing countries found in *PubMed* database from 1996 to 2002. They selected studies that: a) used quantitative methods; b) surveyed participants or parents of pediatric participants in actual trials; c) did not test particular consent interventions; and d) assessed at least one of the domains of comprehension, motivations, and voluntariness. They found four studies from developing countries and sixteen from developed countries that met these criteria. They report that studies from both settings found variable comprehension, especially concerning side effects and randomization. Expectation of health benefits was a major reason for participation for more than half of the subjects in the Gambian Study and in four studies from developed countries. 52% of the subjects in Bangladesh and 20 to 45% of the subjects in six studies from developed countries did not know they could withdraw from the clinical trial.

In a first and preliminary version of this study the authors recognized the need for more rigorous systematic research in the area, but concluded that data do not support claims that the quality of IC is worse in developing countries. However, in its published version they focused on the paucity of data and the difficulty of comparing data on the different clinical trials, taking a cautious stand. They say that: “There are indeed warning signs about participants’ comprehension and whether they are acting voluntarily, but in contrast to some claims, these warnings seem to apply to both developed and developing countries” (Pace et al. 2003).

### The researchers’ view

Is there a different input in the views of researchers from developing countries? Hyder and Wali (2006) published an article about developing countries researchers’ views regarding IC. This work is one of the few empirical studies about IC in developing countries. The article says there is a general positive appraisal of how IC is taken in developing countries. They outline that researchers are “well aware of the importance of consent in health research” (Hyder & Wali 2006: 31). They also point out the need to educate adequately the target community:

“Making the concept of the research project understandable was viewed as critical, as well as allowing for adequate time for education prior to recruitment” (Hyder & Wali 2006: 37). The authors remark that researchers in developing countries “strongly believe in the principle of IC” (Hyder & Wali 2006: 40).

A different style of article about IC in one emerging country and two developing countries was published in *Medical Ethics* (Bhan et al. 2006). This article presents examples from India, Iran and Nigeria. The authors highlight the diversity within and between developing and emerging countries situations. But in the end, they emphasize the importance of IC in research and in clinical practice settings. They also point out to the need to be enterprising and innovative in obtaining it. Interestingly, these authors, coming from quite different developing countries, also endorse IC.

Hence, the views of these articles support the usefulness of IC. However, Hyder and Wali (2006) do report some problematic issues. They note that: a) written consent was not used by nearly 40% of the researchers in their most recent studies; b) a large proportion recommended more flexibility in the ways of documenting IC; and c) 84% of the researchers agreed that a mechanism to measure understanding should be incorporated.

Note that some of the problems just mentioned are related in one way or another to the epistemic conditions of IC, that is, the capacity of understanding adequately the information. Illiteracy can be considered a paradigmatic epistemic condition. It involves the possibility of understanding sophisticated and sometimes written information by people without formal education. Another issue related to this epistemic factor in the process of IC is its “documentation”, in the sense of contributing to make sure comprehension is achieved.

Regarding the first point presented by Hyder and Wali, it is believed that the fact that 40% of the researchers do not use written informed consent seems too high and deserves a thorough explanation which is not provided. While there are comments regarding community consent, non-use of written IC is not a minor issue. IC cannot simply be replaced by “leaders consent” as parts of the article seem to suggest. Attitudes such as the ones Vargas-Parada et al. (2006) present about Mexico are worrisome. This study reports that “most investigators gave only minutes to the patient to make a decision [...]” and refers to a Brazilian study with similar results (Vargas-Parada et al. 2006: 41). The fact that no signature or forms for distribution exists is one thing; another is that of bypassing IC or treating it in a slapdash manner.

It is true that a written form or a signature in oral cultures does not have real meaning. However, there should be clear and accountable ways to give evidence that the IC process was conducted properly, such as through videotaping or having patient advocates present during the process. Illiteracy is no excuse. This kind of problem is related to the epistemic aspect of IC, which focuses on the capacity of understanding. But that a

research subject is illiterate is not an insurmountable obstacle. Illiteracy cannot be considered as a cognitive handicap. It is a contingent fact related to the absence of a written tradition in a certain culture, or the lack of access to such a tradition. None of these are insurmountable deficiencies in a subject's ability to understand complex information. Care should be taken to avoid misconceptions about illiterate persons (Luna 2006). In the specific case of IC this can be handled by offering more sessions, social workers speaking their language, audiovisual help, among other alternatives.

Fitzgerald et al. (2003) published a study in *The Lancet* in which they analyzed two ways of conducting the IC process in a study of HIV transmission to identify host resistance factors to HIV-1 in negative people with sexual contact with HIV positive partners. They prepared a questionnaire – a “comprehension test” – about the study's purpose, voluntary participation, risks and benefits, and knowledge of HIV prevention. In the “standard” model, the physician-investigator took the IC process in one session, communicating the key elements to the research participants and encouraging them to ask questions. In this case only 20% of the research subjects passed the “comprehension test”.

In the second model a social worker took the IC process in three sessions – each of which lasted 30 to 40 minutes – over a period of seven to ten days. The social worker divided the IC into key messages that were communicated verbally and also used visual aids (pictures and anatomical models). In this case, 80% passed the comprehension test and 12% refused during the meetings. More than one-third of the research subjects in both cohorts were illiterate. What this kind of study shows is that participants can comprehend complex information if there is sufficient care. In this vein, illiteracy is not per se a major obstacle.

“Community consent” should be put into perspective. It is clear that in community-based cultures, the community should be involved in the process, that there may be a need for the assent of the community, and that the community may function as a “filter”. But this should not be equivalent to “erasing” the research subject. Each research subject “puts” its body for the research. They should be respected. They do have values, and the possibility of understanding and of choosing, even if one accepts and respects that the implementation of this process can be influenced and modified by their culture. However important the community's involvement may be, community consent cannot replace the person's consent. And this is vital when it is a question of biomedical research or it involves risks to the research subjects.

In practice, respect for the individual and the community may imply some issues to consider: for example, more time that should be taken into account when designing the trial, and deciding who truly “represents” the community. The same applies to the involvement of the “family” – which usually indicates male members. Involving the partner does not mean replacing the woman. Special care should be made to achieve this goal. For

example, the protection of the woman's confidentiality and privacy should be built into the design of the consent procedure. Hyder and Wali do not endorse a particular view on the matter; however, they do quote a respondent that is well aware of the challenges involved:

It may be appropriate or sufficient to ensure community leaders are informed of the research rather than requiring their approval. In communities where leadership could either be aligned to prevailing politics or/and biased towards men, such a requirement may not fulfill the ethical aims as intended (2006: 38).

The second point that Hyder and Wali present concerns the issue of flexibility, a criticism that has frequently been formulated. For example, Onora O'Neill (2006), dealing with research in general, says that “consent procedures are often more formalistic than genuine, because many IC transactions commonly are epistemically inadequate. So there are also reasons to think the practices used to seek IC”.

However, ethical documents, such as CIOMS/WHO Guidelines (2002), explicitly allow for flexibility if the ethics committee approves. Part of the problem regarding the lack of flexibility is the legalistic approach of certain cultures, such as the United States, the lack of education of the Institutional Review Board in the sponsor's country or of the researchers, or the pressure of the pharmaceutical companies. However, flexibility is not tantamount to “anything goes”. It should imply an equivalent procedure by which the research subject understands the research goals, the design and risk-benefit, and can choose whether to participate. To achieve this goal, researchers should consider generating IC in context and not just translating forms. Ideally, local researchers should be involved from the beginning.

There are a number of thoughtful and innovative strategies that can be applied to allow for flexibility and still make it possible to obtain and measure understanding. Some of them were published in the report of an international workshop (Mc Grory et al. 2006). For example, they used tools such as booklets, pamphlets, fact sheets, radio or newspaper advertisements, videos, audio computer-assisted self-instruction, and flip charts. Being HIV prevention trials, they also used some other visual aids, such as blood vials, speculae, product boxes and randomization envelopes to illustrate particular trial procedures (Mc Grory et al. 2006). Some of these strategies are quite burdensome, but are justified when research poses particular challenges and more than minimal risks.

However, a study by Flory and Emanuel (2004) concluded that the use of multimedia and enhanced consent forms has had only limited success. Instead, having a study team member or a neutral educator spend more time speaking one-on-one to study participants appears to be the most effective available way of improving the research participants' understanding. They recognize that more research needs to be done, but this “common sense” and simple strategy sounds quite promising.

Finally, Hyder and Wali acknowledge that a vast majority of researchers ask for a mechanism to measure

understanding. This last point seems to reinforce the importance of achieving the epistemic conditions of IC. In a way it stresses part of what the first two criticisms suggested: the importance of a good process of IC that ensures comprehension. As mentioned above, there are a lot of innovations and mechanisms to be incorporated in order to ensure that the epistemic condition is accomplished and understanding during the IC process is effectively achieved.

## Background conditions and informed consent

Another issue to be outlined regarding IC is related to the description the authors of *Informed consent in international research: perspectives from India, Iran and Nigeria* present. In relation to India, they say:

The public health care system is under-resourced in terms of infrastructure, staff as well as medications. This adversely affects the standard of care that is publicly available [...]. Though most ethics committees are located within academic institutions, in recent years many commercial for-profit ethics committees have also been formed in India, paralleling the phenomenon of increased outsourcing of clinical trials to India. (Bhan et al. 2006: 37).

In major or minor ways, these descriptions reveal something quite common in developing countries: inadequate public infrastructure and a privatization of health care and research. Even if the authors of the above-mentioned article do not go deeply into this problem, these “vignettes” show one of the main issues regarding IC: the background conditions in which it is obtained.

Similarly, an article presenting the limits of IC in the Philippines says that some circumstances, such as poverty, extreme need and marginalization, and the commercialization of medicine, render poor participants in drug trials virtually unable to freely exercise the principle of voluntary IC (Alvarez Castillo 2002). And adds: “Consent to participate in a drug trial when examined in this context loses its value as a tool for the protection of research participants” (Alvarez Castillo 2002: 25).

Resuming the distinction between epistemic and agency problems, it is possible to see that the objections posed previously were fundamentally epistemic. However, the problems presented here are of a different nature. They point to the background conditions in which IC is given, to the possibility of freely exercise the principle of first person voluntary IC.

Against this contextual backdrop, it should seriously be asked how “voluntary” IC truly is when the public health care system is inadequate. For example, analyzing the quality of parental consent in a Ugandan malaria study, the authors point out that many parents felt they could not have refused to participate because their child was sick and they either did not know or did not believe that their child would receive treatment outside the study (Pace et al. 2005).

IC should assume the possibility of rejecting research. But, is this an option when there are no other alternatives or when alternatives imply either participation in research or illness and death? Note that in the Pace et al. study, expectation for health benefits is a major reason to participate. Consider this plus the possibility of therapeutic misconception.<sup>6</sup> These are serious problems when the only available “health care” is research. In many developing countries it is so clear that the only opportunity to obtain at least some health care is by participating in research and that whatever is offered will be a rational choice. But that does not mean that it will be fair; it may be even exploitative (Macklin 2004; Luna 2007).<sup>7</sup>

These last issues with respect to the context of scarcity and desperation are “the challenge” of IC in developing countries. Although there is no clear sign of coercion, we might be able to speak of “quasi-coercion” (Rivera López 2003). This concept acknowledges the difficulties of certain contexts in which the agents must choose among sub-optimal alternatives. In these situations, the choice is not coerced, for agents are not literally forced to choose one alternative over the others, but their decisions cannot be considered completely voluntary. When there is no reasonable alternative, accepting a burdensome choice, such as participating in research, cannot be considered a free choice, for not having chosen it would have meant a greater harm or burden on the agent.

Does this mean IC is “useless” in developing countries? The Philippine article, or the concept of “quasi-coercion”, warn us about the loss of value of IC (Alvarez Castillo 2002). Contrary to this view, IC is useful and valuable, but to be so it has to meet certain pre-conditions. Protection is a major issue. Others are the avoidance of exploitation and a fitting risk-benefit ratio. Only then IC can make sense.

## The theoretical basis

At this point it is interesting to analyze the theoretical basis of IC. The traditional theoretical justification of IC is the principle of respect for persons. One of the leading and first documents that provide an ethical justification is the Belmont Report (United States of America 1979). This document, done by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, developed three basic ethical principles that should govern research with human subjects.

The three basic ethical principles singled by the document are: a) respect for persons; b) beneficence; and c) justice. This article will focus on the principle of respect for persons because it is the one related directly with IC. This principle incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents; second, that persons with diminished capacity should be entitled to protection. So this document says:

An autonomous person is an individual capable of deliberation about personal goals and of acting under the

direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. (United States of America 1979, Section B).

But the Belmont Report will also point that not every human being is capable of self-determination: "[...] Some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated" (United States of America 1979, Section B). This second aspect of the principle of respect for persons is very important because it recognizes not only autonomy but also the need for protection when this autonomy cannot function partially or wholly.

Another problem that this document considered was entering a research voluntarily. It took as an example the involvement of prisoners in research. Regarding this issue, the document said:

On one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. (United States of America 1979, Section B).

In this same document, informed consent is analyzed as containing three elements: information, comprehension, and voluntariness. When speaking of information, the report lists some items to be informed about that most codes of research establishes (United States of America 1979, Section C). The point dedicated to comprehension states that the manner and context in which information is conveyed is as important as the information itself. It also outlines that, because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subjects' capacities. Note that these two first elements are the theoretical analysis of the epistemic condition presented in this article.

Regarding the last point, voluntariness, the Belmont Report points out that it requires the conditions free of coercion and undue influence. And it says:

Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable. (United States of America 1979, Section C).

When considering cases of unjustifiable pressures, the document says it usually occurs "when persons in positions of authority or commanding influence – es-

pecially where possible sanctions are involved - urge a course of action for a subject" (United States of America 1979, Section C).

The kinds of examples considered within this document are tailored by the cases mentioned in the first part of this article, as well as the background conditions that motivated the need for a serious reflection in research ethics. For instance, when speaking of voluntariness the dilemma is presented by prisoners, isolated people in institutions where their rights may be overridden. Not only there is still present the shadow of the Nazi experiments, but also all the research done in the gilded age that involved persons living in health institutions (elderly people, orphans or children with mental disabilities). Consider also that even when it is recognized the importance of protecting research subjects, this factor is directly connected with the capacity of deliberation. The accent seems to be focused on the description of persons with diminished capacity (that is, the epistemic condition) as the ones that should be entitled to protection.

But this is just one case; there are other situations that weren't sufficiently present at that time. Only in passing does the Belmont Report consider the situation of inducements to specially vulnerable people. And a quick reading of the theoretical foundations of IC may bypass the need for an adequate protection in certain cases that go beyond the epistemic situations and speaks of voluntariness – the third element outlined by the report.

## Problematic assumptions

There is a reductionist justification of IC that may imply a certain view of the research subject, which sometimes is presented in an overly simplistic and idealized way. If one focuses only on the autonomy part of the justification, it seems that the sole important feature is the capacity of deliberation. That is, only the epistemic problems are answered. Note that to respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. If one considers only the deliberative factor, the process of informed consent can be equated to a contract, and the research subject to a contractor, that is, an idealized agent acting in the vacuum. This stance implies an offer to participate in certain activity, the information regarding options and the free choice of the person to engage in that activity, as if options and the capacity for free choosing were unproblematic.

But the Belmont Report speaks of the principle of respect for persons. This implies not only autonomy, but also protection. However, in the report this protection is exemplified mainly with diminished intellectual capacity, that is, with epistemic deficiencies. If just this is taken into account, one may have a reading of the principle of respect for persons that may not take sufficient consideration of the voluntariness element that should be involved. And even if the Belmont Report points out voluntariness, it is mostly read as non external coercion or excessive,

unwarranted, inappropriate or improper reward in order to obtain compliance. Frequently this is interpreted as avoiding giving gifts or payments that may interfere with voluntariness. Or such as the example that is considered in the report itself, alterations of voluntariness given that the IC may be asked by someone in a position of authority that may unduly influence the decision. However, there are other subtler ways of interfering in the process of IC that concern voluntariness and the agent's capacity of free action. If IC is justified only by the need for an autonomous decision, there may be the risk of assuming an overly simplistic view of research subjects.

Debates already exist about the conceptualization of the research subject (Luna 2007). In these discussions, some ideas of Swazey and Glantz (1982, 1995) are developed. These authors offer an interesting analysis of society's obligations and compensation to injured research subjects. They are not thinking in the concept of a research subject specifically, but their analysis could be easily extrapolated to this issue. They ask if it is possible to consider research subjects as altruistic heroes, giftgivers, willing contractors, or victims. It is observed that the kind of model used in order to think of what it is to be a research subject will affect the way society should treat research subjects. The two models which can be taken from the authors' proposal are those in which the research subjects are seen as contractors and/or as victims.<sup>8</sup>

The model of the contractor follows the pattern of the businessman striking a bargain: so long as the negotiation process is just, the contractors have a right to no more than what they bargained for.<sup>9</sup> Victims, on the other hand, are those who were treated unjustly or harmed without their consent. They can be especially vulnerable or the target of exploitative behavior and can do little to avoid these harms.

Is the willing contractor model acceptable? It appears to be so in the case of English or Swedish research subjects, who can access a universal healthcare system. However, even in these cases, it is necessary to consider problems as therapeutic misconception, as well as the emotional stress caused by the extent of available therapeutic alternatives. Patients with access to current therapies are better off than those without. They can test the best current therapy or participate in a trial, weigh the risks and benefits, and decide. This may be an accurate description if the severity of some diseases and the stress that the patient may be undergoing are not taken into account. However, considering research subjects as mere contractors seems too simplistic. When IC is conceived as a contract to be negotiated, an inadequate vision of the research subject is being held.

The model of a mere contractor does not work. And this is more so in the case of someone who lives in absolute poverty and/or in a poor country. How can patients bargain when their only access to treatment is a clinical trial? Note also that, when thinking in the contractor image, it is not considered that these are not perfect contracts. They occur in the real world and depend on the negotiating power of the actors. Onora

O'Neill (1996) indicates how important the possibility of refusal or renegotiation is to check whether consent is not a mere formality. In these cases, the actual possibility of refusal is vital. It seems something is being missed if only having a "contract" is focused.

Should, then, the image of the victim be endorsed? In their analysis, Swazey and Glantz assume that victims are the ones which lack total consent (victims of the Nazis or from Tuskegee). Those cases are clearly unethical models and cannot be justified. In these cases, it is evident that some form of coercion took place, and victims appear to be entitled to compensation (Swazey & Glantz 1995).<sup>10</sup> However, the focus should not be on such extreme cases, which are obviously unethical. As mentioned above, there are other situations where "victims" can be found. Vulnerable people or with scarce resources are likely to be victims, but have not been actually harmed or coerced. So, while harm and coercion requires a fair compensation, quasi-coercion may require other measures. Therefore, instead of thinking in compensations, it is necessary to think in adequate protections.

Hence, a mixed model has to be considered: one where the role of the research subject as a contractor is respected, but where its possibility of being a victim is also taken into account. The concept of a research subject should reflect the two images. There are aspects of a willing contractor (therefore, the importance of informed consent), but also, and in many cases, the person may share the features of a victim (therefore, the importance of suitable protection). In this sense, in each research situation the prevailing model should be evaluated: whether the individual is a willing contractor or a victim; or how much of a contractor and how much of a victim is present in that case. This evaluation will help establish the correct safeguards and protections.

Other "subtle" factors that seem to weigh should not be forgotten – for example, vulnerability. Research ethics cannot avoid this factor. In this sense, the conditions in which IC is given are fundamental: it has to be clear that IC is truly voluntary and not the consequence of the unavailability of other options. But these last issues are related to new situations in which multicentre research occurs. One is not facing the gilded age problems in research, but those that a globalized world present: for example, the challenge of replicating a protocol in Argentina, Bolivia, Brazil, Thailand, or Uganda that was designed in Johns Hopkins or Paris. These are countries with very different socio-economic situations and where the context in which IC is given merits attention. The theoretical justification of IC has to consider these other aspects, which were suggested in the Belmont Report, but not sufficiently stressed. The deliberative aspect of IC is covered by the autonomy element of the principle of respect for persons, but the voluntariness and agency capacity of the research subject cannot be forgotten.

The two levels of problems pointed in this article, the epistemic and the agency related ones, are clearly illustrated in a non-reductionist view of the justification of IC, as well as of the research subject. Hence, in this

non-reductionist view, the mixed model for the conceptualization of a research subject allows for understanding and giving an answer to the two levels of problems that IC in developing countries presents today.

## Conclusion

In this article it was presented how IC has evolved and how it was tied to classic cases of research ethics. It is believed that these first cases also shaped the theoretical foundations of IC and that a quick reading of the Belmont Report may not consider the voluntary element regarding subtle factors, such as the scarce resource context. The latter is an unavoidable issue in research in developing countries today.

It was shown that epistemic problems are not insurmountable obstacles. Illiteracy can be overcome and the process of IC should continue to be improved. Even more, sophisticated methods may not be necessary; the common sense and “low tech” mechanism of spending more time talking one-on-one to study participants seems promising. Flexibility can be incorporated with a close and suitable protection of research subjects as well as mechanisms to measure understanding.

In relation to voluntariness and agency, the least that should be done in order to carry out ethical research in developing countries is to consider the context and the conditions of scarcity where research is offered in order to provide adequate safeguards. In this sense, an adequate risk-benefit ratio – one that will not place individuals at risk and where proper safeguards are already in place – is basic. Among other safeguards, it is vital to consider research committees, and local research committees in particular. They have a great responsibility in reviewing the protocols, and should be strong and independent enough to freely accept the research proposals, request changes in them, or reject them.

Scarcity is a big issue. It invites exploitation, but this is not a challenge to IC in developing countries alone, but to research in developing countries in general. However, this does not mean that research in these countries should be stopped. Research is of critical importance for developing countries. But there should be a clear awareness of the challenges and problems involved. For example, what the obligations during and after research are; how relevant the research is for that population; and if the fruits of research will be made available to the community. IC is highly important in research; it is a necessary condition, but not a sufficient one. Above all, it is crucial to avoid exploitation, to treat research subjects respectfully. Only then can a mindful and context-sensitive IC process be a useful tool for developing countries.

## Notes

1. In contrast to what was sustained by way of a post-war apology, the physicians were never forced to conduct these experiments. They volunteered, and, in some cases, Nazi officials had to check the zealous physicians from continuing even more ambitious experiments.

2. Beecher (1966) reported that only two of the original fifty protocols so much as mentioned obtaining consent.

3. Baruch Brody (1998) illustrates this same point and adds data from other sources. For example, he says that M. H. Pappworth published Human guinea pigs, in which he alleged similar problems in British research. In Canada, much attention was focused in the 1960s on the Halushka case, in which a subject in a study who had not received adequate information about what was involved in the study suffered serious injury after the use of a new drug and invasive monitoring. In New Zealand, investigations in the 1980s focused on research in the 1960s and 1970s in which women with cervical cancer in situ were left untreated to study the natural history of the disease. As was expected, many developed invasive carcinoma from which some died.

4. This is a reference to Nigeria.

5. Pace C.; Grady C.; Emanuel E. The quality of informed consent for clinical research: a comparative review of empirical data from developing and developed countries. Draft paper. With Emanuel's permission to comment on it.

6. This problem will not be approached here.

7. This is a topic only lately explored.

8. The other two images, the altruistic hero and the giftgiver, will not be considered. Heroes volunteer and assume risks for someone else's sake. Since heroes are not supposed to seek reward, society has no obligation to compensate heroic research subjects. Likewise with giftgivers, although such donors may not be morally entitled to compensation, society may desire to return the favor by compensating their injuries.

9. The conception of justice involved in this idea is purely formal or procedural. It follows a libertarian model of justice, as for example, Robert Nozick proposes.

10. Victims have a strong moral claim on compensation, especially where society has facilitated research or benefited from it.

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