INFORMED CONSENT OF HUMAN SUBJECTS: A REVIEW

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ABSTRACT: Informed consent is a vital part of the research process, and as such entails more than obtaining a signature on the consent form. Researchers or investigators must educate potential subjects to ensure that they can reach a truly informed decision about whether or not to participate in the research. Their consent must be given freely, without coercion, and must be based on a clear understanding of what participation involves. Only then it can be regarded as 'informed consent'. Although a relatively recent phenomenon, the role of informed consent in human research is central to its ethical regulation and conduct. However, guidelines often recommend procedures for obtaining informed consent (usually written consent) that are difficult to implement in developing countries. This paper reviews the guidelines for obtaining informed consent and also discusses prevailing views on current controversies, ambiguities and problems with these guidelines and suggests potential solutions.

key words: Informed consent, Human subjects

INTRODUCTION: The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who will not benefit personally from the research and for those for whom the research is combined with care.

METHODS: The article was written in Research and Training Monitoring Department of BCPS is located in Dhaka, Bangladesh during research ethics course of Bangladesh Bioethics Society in collaboration with National Institutes of Health, Bethesda, Maryland, USA through video conferencing on September 25 through November 11 of 2013. In this study the systematic literature search has performed published during 2000 to 2013, using four database including MEDLINE, PUBMED, HINARI and Google Scholar. Only studies that focused informed consent in human subjects were included in this review process. A total of 30 articles were retrieved and 16 of them were selected for review.
All protocols were cited on the World Wide Web (WWW) by applying the key words; Informed consent of human subjects.

INFORM CONSENT:

Assent of the child: The willing cooperation of the child should be sought, after the child has been informed to the extent that the child's maturity and intelligence permit. The age at which a child becomes legally competent to give consent differs substantially from one jurisdiction to another; in some countries the "age of consent" established in their different provinces, states or other political subdivisions varies considerably. Often children who have not yet reached the legally established age of consent can understand the implications of informed consent and go through the necessary procedures; they can therefore knowingly agree to serve as research subjects. Such knowing agreement, sometimes referred to as assent, is insufficient to permit participation in research unless it is supplemented by the permission of a parent, a legal guardian or other duly authorized representative.

Some children, who are too immature to be able to give knowing agreement, or assent, may be able to register a 'deliberate objection', an expression of disapproval or refusal of a proposed procedure. The deliberate objection of an older child, for example, is to be distinguished from the behaviour of an infant, who is likely to cry or withdraw in response to almost any stimulus. Older children, who are more capable of giving assent, should be selected before younger children or infants, unless there are valid scientific reasons related to age for involving younger children first.

Consent is an important area and one that the reviewer and the committee will focus when reviewing the application. Consent must be informed and freely given. There must be no coercion. Participants must have the capacity to consent and the right to withdraw without penalty and providing an explanation. It must be ensured that all relevant information is included and it must be explained clearly what the participants will be asked to do on the participant information sheet. Participants should be told why they have been selected to take part and how many people have been approached.

As part of the information given to the participants, it must be stated that the research study has been approved by the ethical committee of the BMRC. Participants must be informed of any risks. There will always be some, is not acceptable to say there are no risks. Participants must also be informed of their legal rights, the storage and destruction of data and right to withdraw from participation in research at any time, without giving a reason. Participants must also be provided with contact details for further information, which should include a postal address and a telephone number where a person will be available at certain time to answer questions. Taking consent must be viewed as a process, not just the person reading the information sheet and signing a consent form. There is evidence that people understand much less than what they are thought to understand. The participant information sheet should therefore be checked for readability.

The committee will also want to be assured that the participants are being adequate time to decide whether they wish to take part and have the opportunity to discuss the research with family and friends. If direct quotes from participants is going to be used for dissemination, or recording using audio or video equipment, this must be
stated on both the participant information sheet and as one of the statements on the consent form. If personally identifiable information is going to be used for dissemination for example photographs, participants must be given the opportunity to be contacted on each occasion that these will be used, in addition to taking their consent.

It is good practice to notify all participants regarding the last approximate date it will be possible to withdraw their data (for example, prior to publication). It will need consideration whether participants’ data will still be useful if they decide to withdraw. If this is the case, they will need to consent for its use, they can therefore be given the option to withdraw and also have their data withdrawn, or to withdraw but state that they will allow their data to be used. If a focus group is being carried out, it will not be possible to withdraw one person’s data following the intervention without removing the data for all the participants, because what one person says will affect the responses from others.

It must be made clear on the participant information sheet that it will not be possible to withdraw data in this case. It is also necessary to make it as easy as possible for people to withdraw, bearing in mind that they might not feel comfortable telling the investigator directly that they no longer wish to participate. Options, such as posting a slip, will need to be included.

One should also guard against unrealistic assurances to participants about data being anonymous. It is essential that every effort is made to remove all identifying information relating to participants prior to dissemination. Information that could identify people is not limited to their names. It is sometimes possible with case studies that people may be identified. This needs to be made explicit in the participant information sheet. The words anonymous and confidential are often confused. These must be refereed to correctly on the participant information sheet.

It must be ensured that the documentation is inclusive. For example if the research involves people who cannot speak or write English, the documentation needs to be translated (a professional translator needs to be employed unless the investigator is fluent in Bengali). Consideration for people with special needs, for example, dyslexia, will need to be included and the provision for alternative formats of documentation should be made.

If research is related to other people, for example asking questions about family member’s participants, consent or permission from them should also be taken, as applicable. The assumption should not be made that because participants are revealing information about family members (as opposed to others outside their family) that this will be all right. Even if research is carried out that does not ask participants about other people. Consideration should be given beforehand whether others are likely to be discussed. If so, it should be considered whether consent should be taken from them.

**INFORMED CONSENT WILL BE OBTAINED:** In order to approve research involving adults as study participants, the IRB must determine that legally effective informed consent will be sought and obtained from each prospective study participant or the study participant's legally authorized representative, unless informed consent requirements can be waived or altered under Federal regulations. Any such waiver or alteration must be consistent with applicable Federal and State laws and regulations.
Where consistent with state law, Case IRB policy recognizes as legally authorized representatives:

1. Persons appointed as health care agents under a Durable Power of attorney for HealthCare;
2. Court appointed guardians;
3. Next of kin in the following order: spouse, adult child, parent and adult sibling.

However, Case IRB policy limits the conditions under which the IRB may approve the use of consent from legally authorized representatives.

INFORMED CONSENT PROCESS: The ethical foundation of informed consent is the principle of respect for persons. Competent individuals are entitled to choose freely whether to participate in research, and to make decisions based on an adequate understanding of what the research entails. Decisions for children or adults who lack the mental capacity to provide informed consent should be made by an authorized surrogate decision-maker.

RECs should examine the process through which informed consent will occur, as well as the information that will be provided. RECs may waive the requirement of informed consent only when doing so is consistent with international guidelines and national standards.

While informed consent to research is important, the fact that a participant or surrogate may be willing to consent to research does not, in itself, mean that the research is ethically acceptable.

Informed consent is an essential component of a research project. Obtaining informed consent enables research and clinical procedures to be conducted both ethically and legally. Consent is considered ‘informed’ when given by a person who understands the purpose and the nature of research, and what is required of themselves as participants, in addition to the potential benefits and risks resulting from the study. Elements of valid consent include the capacity of participants to provide consent, disclosure of necessary and important information, freedom to choose to participate without coercion (i.e., freedom not to participate), and consent of participants.

Informed consent is a vital part of the research process, and as such entails more than obtaining a signature on the consent form. Researchers or investigators must educate potential subjects to ensure that they can reach a truly informed decision about whether or not to participate in the research. Their consent must be given freely, without coercion, and must be based on a clear understanding of what participation involves. Only then it can be regarded as ‘informed consent’.

The process of educating subjects about the study begins during initial contact and continues for the duration of their participation. Thus, information conveyed through advertisements, recruitment letters, pre-screening phone calls, study description sheets as well as written informed consent documents and discussions must be understandable to the subjects and should contribute to their understanding of the research. Technical and medical terminology should be avoided or explained in “lay” language, and materials should be written at an 8th grade reading level or lower. Non-English speaking subjects must have information presented in a language they understand. The Partners Human Research Committee (PHRC) must approve written and oral information (including recruitment materials) provided to subjects before and during the informed consent process.
The consent discussion should begin sufficiently in advance of the initiation of study-related procedures to allow potential subjects time to reflect on the potential benefits and risks and possible discomforts of participation. The following method is preferred, though clearly it may need to be tailored to the circumstances of individual studies and may not be appropriate or feasible in all situations. First, potential subjects are given general information about the research and if they are interested in learning more about the study, they contact study staff. The investigator then meets with the potential subject to review and to discuss the details of the research study using the informed consent document as a guide. This discussion should include all of the required elements of informed consent, e.g., the purpose of the research, the procedures to be followed, the risks and discomforts as well as potential benefits associated with participation, alternative procedures or treatments, if any, to the study procedures or treatments, and provision of compensation, if any, due to unwanted damage/disability of the research subjects.

Preferably, potential subjects are then given a copy of the informed consent document to take home so they can carefully read the document and discuss the research with their family, friends and/or physician and develop questions to ask at their next meeting with the research staff. Subjects must always be given the opportunity to ask questions and have them answered by the investigator and, whenever possible, to consult with friends/family and/or their physicians. Once they have read the consent document and their questions are answered, if they agree to participate in the research, they sign and date the informed consent document. However, subjects must be asked as well for written authorization for the use and disclosure of their identifiable information for research.

Special consideration must be given to the timing of the consent process when the subject population includes patients who will be same-day admissions for surgical procedures or who present for diagnostic or other tests, such as cardiac catheterizations or radiological examinations. Clearly, the time frame for the consent process will be more limited in these situations. Generally, the investigator should allow potential subjects at least 12 hours to consider participation. Whenever possible, the patient’s physician should be asked to provide potential subjects with information about the study well in advance, for example, when the surgery, test, or examination is scheduled.

With few exceptions, the informed consent of subjects, whether patients or healthy volunteers must be obtained and documented in writing before the start of any study-related procedures that include screening tests and examinations done solely to determine their eligibility for the study. Informed consent is to be obtained directly from each subject, with the exception of children (as there are some special regulations for children as research subjects) and adults who have impaired decision-making capacity. Once the informed consent document has been signed, subjects are considered enrolled in the study.

**INDIVIDUALS WHO CAN OBTAIN INFORMED CONSENT:** For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator listed on the protocol must obtain informed consent. Study nurses or other study staff may assist in the consent process, but physicians should be actively involved in the consent discussions and should not delegate this vital investigator function. It is the investigator’s responsibility to ensure that proper informed consent is obtained from every subject according to the procedures approved by the PHRC. For minimal risk studies and very carefully selected studies involving more than
minimal risk (but not investigational drugs/devices), it may be appropriate for study nurses or other study staff to obtain consent, with “back up” provided by licensed physician investigators. The PHRC will allow a licensed nurse or non-licensed physician investigator to obtain informed consent if that nurse or non-licensed physician would be permitted, in a clinical setting, to perform the procedures for which consent is required. If the investigator proposes that other than licensed physician investigators obtain informed consent, the rationale and justification for this approach and the qualifications and training of the relevant study staff must be submitted to the review and approval7.

If subjects are to be enrolled from among the investigator’s own patients, consent procedures must be put in place to ensure that subjects do not feel obligated to participate because the investigator is their treating physician. There is always concern about the possibility of patients feeling obligated to participate because it is their physician who is doing the asking. While the PHRC does not have an absolute prohibition about physicians obtaining consent from their own patients, researchers are asked to think about this issue and address it. There are many possible ways to do this. One can contact the patient in writing initially, and allow him/her to make the first contact if interested. One can ask a physician colleague to present the study to a patient to try to make it more impartial. One can have a nurse or colleague re-contact the patient after the investigator has had the consent discussion and offer them an opportunity to ask additional questions, raise concerns, or opt out, with someone who is not their physician7.

Obtaining Parental/Legal Guardian Consent for Children: Federal regulations require that consent to participate in research on behalf of a child be provided by a parent or an individual authorized under applicable state or local law to provide consent on the child’s behalf to general medical care. Under Massachusetts law, a parent is generally authorized to consent to general medical care on behalf of their child. However, in some circumstances (such as when both parents are deceased), it may be necessary to identify another individual with this authority (for example, a court-appointed guardian). Before an investigator allows an individual other than a parent to consent on behalf of a child, the investigator should document the basis for the individual’s authority to consent on behalf of the child to general medical care and place any relevant documentation in the research file. In situations when it is unclear under state law who has the authority to provide consent to general medical care on behalf of a child, and thus who can consent to the child’s participation in research, the PHRC will consult with the Office of General Counsel as needed7.

Under the federal regulations, where consent to the research is to be provided by a child’s parent and the research involves no greater than minimal risk or greater than minimal risk, but with the prospect of direct benefit to the subjects, the PHRC may decide that consent of one parent is sufficient. However, when the research involves greater than minimal risk and no prospect of direct benefit to the subjects, permission must be obtained from both parents, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when one parent has legal responsibility for the care and custody of the child.7 In addition to permission of the parent(s) or guardian, assent to participate in the study must be obtained from each child age 7 years or older who, in the opinion of the investigator, is able to provide assent based on their age, maturity or psychological state. When the PHRC determines that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children involved in the research and the intervention or procedure is only available in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even when the children are capable of
assenting, the PHRC may waive the assent requirement as described elsewhere in this document [Alteration or Waiver of Elements of Informed Consent].

When obtained, assent must be documented in writing using the PHRC-approved consent/assent form. When assent is not obtained, the investigator must document his/her rationale in the research records.

**Minors Who Can Give Legally Effective Informed Consent:** Under Massachusetts State law and MGH/BWH clinical policies, some minors (less than 18 years of age) can provide legally effective consent for their own medical care, in certain circumstances, without parental consent or knowledge and therefore may not meet the DHHS and FDA definition of “children” and the requirements of Subpart D may not apply. “Emancipated” minors, i.e., those who are married, widowed or divorced, or have a child or are pregnant (or believe themselves to be), are in the armed forces, or living apart from their parents and managing their own affairs, can provide informed consent for their own medical care. Minors in Massachusetts may also give consent to research procedures that involve:

- psychiatric treatment, if the minor is 16 or over;
- treatment of drug dependency, if the minor is 12 or over; and
- treatment of certain diseases dangerous to public health (VD and others).

Because these minors nonetheless may represent a vulnerable population, the IRB will review all consent issues involving these minors on a case-by-case basis to ensure that any required additional protections are met. For example, although these minors may be allowed to consent to the research, the IRB may decide that permission of a parent or other individual is appropriate either instead of or in addition to the minor’s consent.

If the PHRC approves the obtaining of informed consent from specified minors, informed consent follows generally the same procedures that are being followed for adults. The investigator must also document the specific circumstances that justify designating a particular subject less than 18 years of age as capable of providing consent to the treatments and procedures involved in the particular research.

**Language and literacy:** The language spoken by study participants and literacy levels of study populations are essential factors to consider in developing tailored approaches to informed consent. Although it may seem obvious for investigators to develop linguistically appropriate consent documents using clear and simple language, the use of complicated biomedical and scientific language, and lengthy and cumbersome consent forms, continue to be challenging for participants, particularly in low-income settings around the world. Comprehension of information provided in consent forms and consent discussions is foundational to voluntary participation. How much information is necessary - and in what format for individuals to understand the implications of joining a genomic study? These are important issues to consider in tailoring informed consent processes for genetic and genomic research. For example, in our podoconiosis project, we observed that the majority of participants did not understand that information in the informed consent document and discussion was provided to enable them to make a decision about participating in the study. Instead, participants thought the information was provided as a form of health education.

**Use of a Subject Advocate:** In certain situations, the PHRC will require the use of a subject advocate in the consent process. The subject advocate is an individual who has no vested interest in the research and who agrees to act as
an impartial third party in the consent process. When a subject advocate is appointed, the subject advocate is expected to act in the best interests of the subject by sharing in discussions with the investigator and with those responsible for giving consent. Individuals who might fulfill this role include the subject's primary care physician or other health care professional not involved in the research. The subject advocate is responsible for ensuring that the subject understands the research procedures and the risks and potential benefits of participation and that his/her consent is free and voluntary. When a subject advocate is used, the subject advocate must sign and date the consent form. 

SITUATIONS IN WHICH THE USE OF A SUBJECT ADVOCATE MAY BE REQUIRED INCLUDE:

1. When the risks to subjects are significant and the subject is the patient of the investigator and, as such, may feel obligated to participate; or
2. When consent is to be obtained in the emergency room or in an emergency situation when the time frame to obtain consent prior to start of study-related procedures is limited; or
3. When surrogate consent is to be obtained for research involving more than minimal risk with the potential for direct benefit to the subject.

DOCUMENTATION OF INFORMED CONSENT: In almost all cases, investigators must document the informed consent process by use of a written consent document (research consent form) signed and dated by the subject or his/her legally authorized representative (or surrogate) and the investigator (or study staff if approved by the PHRC) who obtained the subject's consent. When the research will begin on the same day that informed consent is obtained, the PHRC recommends recording time of consent in addition to date of consent to document that informed consent was obtained prior to any study-related procedures. In certain situations, the PHRC may approve a waiver or alteration in the consent process (see below). 

The research consent form must include the basic elements of informed consent outlined in Appendix A. The entire text of all research consent forms must be approved by the PHRC as part of the review process. The effective date of the PHRC-approved consent form and expiration date of PHRC approval (one year or less) are noted in the footer added to the research consent form by the Human Research Office staff. Subjects must be given and sign the most recently approved version of the research consent form. Outdated and/or expired research consent forms must not be used in the consenting process and to document informed consent. 

Usually, three copies of the signed and dated research consent form are needed. The original signed and dated research consent form should be retained in the research records. A copy of the signed and dated research consent form must be given to the subject and a copy placed in the subject’s medical record, if relevant to his/her ongoing medical care. If the study involves sensitive research, (e.g., alcohol or drug use, some genetic studies) a copy of the research consent form ordinarily should not be placed in the subject’s medical record. (If the sensitive study involves a drug or otherwise might implicate care decisions, the investigator should discuss with the IRB how best to make this information available to a caregiver with a need to know).
To further document and facilitate clarification of any future questions regarding the consenting process, the investigator should consider including the following information in a clinic chart/progress note/other source document: that XX study was explained, questions were answered (if any), subject agreed to participate and signed the consent form, and a copy of the signed consent form was given to subject. This note should be signed and dated by the person obtaining consent.

**WAIVER OF WRITTEN INFORMED CONSENT:** The PHRC may waive the requirement to document informed consent with a signed written informed consent document for some OR all subjects if it finds either: (1) that the research is not subject to FDA regulations and the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether s/he wants documentation linking him/her with the research, and his/her wishes will govern; if the PHRC approves waiver of signed consent based on consideration (1), the full consenting process for these subjects including being given a written informed consent document embodying all the elements of informed consent remains the same except that the subject will have the option to not sign the consent document or have information linking them to the study placed in their medical file. OR (2) that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. If the PHRC approves waiver of the requirement to obtain a signed written consent form based upon consideration (2), investigators must fully inform prospective subjects about the study, answer their questions and obtain their verbal informed consent. In lieu of a written consent form, the PHRC may require the investigator to provide subjects with a written statement regarding the research. (To obtain oral authorization for use/disclosure of identifiable information under the Privacy Rule, see Obtaining Oral Authorization For Use and Disclosure of Identifiable Information.)

When the PHRC approves waiver of the requirement to obtain a signed written consent form based upon consideration (2), the investigator should consider including the following information in a clinic chart/progress note/other source document: who was approached, for what study, who explained the study, brief summary of what was explained, subject (or surrogate) expressed an understanding of the research study and willingness to participate, questions (if any) were answered to the subject’s satisfaction, subject agreed to participate, and written information about the study was given to the subject, if appropriate. This note should be signed and dated by the person obtaining consent.

**ALTERATION OR WAIVER OF ELEMENTS OF INFORMED CONSENT:** The PHRC can approve a consent process that does not include, or that alters, some or all of the elements of informed consent or even waive the requirement to obtain informed consent provided the PHRC finds that the research is not subject to FDA regulations and documents that all of the following requirements are met:

1. the research involves no more than minimal risk to the subjects;
2. the waiver or alteration will not adversely affect the rights and welfare of the subjects;
3. the research could not practicably be carried out without the waiver or alteration; and
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation\(^7\).

Requests for alterations in or a waiver of informed consent requirements should be made in writing and justified by addressing each of the 4 points above. (For waiver or alteration of authorization under the Privacy Rule, see Waiver and Alteration of Informed Consent and Authorization for Research)\(^7\).

Obtaining New Consent and/or Notifying Subjects of Major Changes to any Component of the Informed Consent Document. Subjects should be asked for new consent i.e. through the investigator’s explanation and request to sign a revised, PHRC-approved consent form -- when they are actively engaged in the research and there have been major changes to any component of the consent form, e.g. drug dose(s), device, study procedures, risks and discomforts, benefits, and alternatives. This is paramount if knowledge of the new information might affect subjects’ willingness to continue participation. Subjects should also be notified of a change of the principal investigator or contact information; however, in most cases this type of change can be adequately communicated in a letter. Please note that a change in co-investigators and/or study staff is not considered a major change requiring new consent or notification.\(^7\)

It is important to note that as part of the review of amendments to the protocol and/or informed consent document, the PHRC will determine whether the change(s) require obtaining new consent from subjects enrolled in the study.

Examples of when a subject should be asked for new consent in writing:

- the Procedures section of the consent form has been revised to include a new procedure that the subject will be asked to undergo, e.g., genetic testing, cardiac catheterization, biopsy, colonoscopy, mammogram, ultrasound, etc. An investigator may not perform a procedure on a subject without new consent if the procedure was not mentioned in the original consent process and form.

Subjects should be given the following information in a timely manner so that they can make a fully informed decision about whether they wish to continue their participation. The greater the import of the new information, the more quickly subjects should be made aware of it.

- the Risks and Discomforts section of the consent form has been revised to include a newly identified serious adverse event
- the Risks and Discomforts section of the consent form has been revised to include a change in the severity or frequency of a serious expected event
- the Alternatives section has been revised to include newly identified alternative therapies or diagnostic tests
- the Procedures and Alternatives section have been revised to include a change in FDA approval status of the drug or device being studied

Examples of when the PHRC may approve a letter being sent to notify the subject of the change include:

- the principal investigator has been changed
- the study contacts have been changed and/or the contact telephone numbers have been changed
- the subject has completed the study interventions and is in the follow-up phase of the study or in some cases has completed the study, and the information is such that learning it would not materially affect the subject’s decision to continue participation in follow-up\(^7\).
APPENDIX A – BASIC ELEMENTS OF INFORMED CONSENT: 45 CFR 46.116(a)(b) and 21 CFR 50.25(a)(b)

The following information about the study must be provided to research subjects when obtaining informed consent:

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
2. A description of any reasonably foreseeable risks or discomforts to the subject;
3. A description of any benefits to the subject or to others which may reasonably be expected from the research;
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained, and when applicable, that notes the possibility that the Food and Drug Administration may inspect the records;
6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

When appropriate, the following information must be provided to each subject:

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
3. Any additional costs to the subject that may result from participation in the research;
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
5. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and
6. The approximate number of subjects involved in the study.

NOTE: Any informed consent, whether written or oral, must not include exculpatory language such that the subject is made to waive, or appear to waive, any of his or her legal rights or to release the institutions or its agents, the investigators, from liability or negligence.

Examples of exculpatory language:
By agreeing to this use, you will give up all claims to personal benefit from commercial or other use of these substances.

I voluntarily and freely donate any and all blood, urine, and tissue samples to the U.S. Government and hereby relinquish all right, title, and interest to said items.

By consent to participate in this research, I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the research.

I waive any possibility of compensation for injuries that I may receive as a result of participation in this research.

DISCUSSION: Informed consent is universally recognized as a central component of ethical conduct in scientific research. Investigators working with diverse populations throughout the world face myriad challenges. The application of standards for informed consent can be daunting for researchers when they face the pragmatic constraints of the field and the reality of cultural beliefs about consent that may be in direct conflict with regulatory requirements. This paper explores cultural and social factors underlying informed consent for health research with diverse populations in international settings. Sociocultural influences on comprehension of information, perceptions of risk, and beliefs regarding decisional authority are reviewed. The implications of power inequities between study sponsors, researchers and participants are also considered. Issues associated with the development and preparation of consent forms, including translation and documentation are highlighted. Recommendations for good practices are outlined and future directions for research are explored.

Since the Nuremberg trials, informed consent (IC) has been recognized as a basic ethical requirement for research involving human participants. Such consent encompasses two distinct elements: (1) researchers communicate detailed information about study procedures, outcomes, risks, and benefits for the participating individual or community, and (2) after understanding and careful consideration, the participants consent to take part under these conditions. However, the suitability of IC for genomic studies has been recently challenged. Because the research protocol for such studies may evolve over time, the condition in IC of providing detailed information for a well-defined protocol is not easily satisfied.

Genetic and genomic research requires access to human DNA from biological specimens, which can be stored and used in multiple research studies. Access to stored biospecimens for genetic and genomic research is critical because understanding genetic variation and its association with common and complex disorders on a genome-wide scale requires large sample sizes to achieve sufficient power. Biospecimens are most useful when linked to clinical and other phenotypic information about the sample source. This has been accomplished in some countries by the creation of national biobanks. In addition to the proliferation of population-based biobanks, many investigators, pharmaceutical companies, and institutions are collecting and storing biological specimens, clinical data, and genetic information in local and regional repositories. Often, cell lines are made so that the specimens can be studied indefinitely, and resulting DNA data are made broadly available for secondary analysis through publicly accessible or restricted databases. How specimens and data are collected and stored, for how long, by whom, and for what purposes vary tremendously. However, most genetic and genomic research projects share several common features.
that challenge the established norms of informed consent. In this article, we discuss these challenges, explore specific elements of informed consent for genetic and genomic research, and consider alternative consent models that have been proposed. All of these models attempt to balance the obligation to respect and protect research participants with the larger social interest in advancing beneficial research as quickly as possible.

Marshall PA et al. highlights the need for more effective approaches and interventions to improve comprehension of consent for genetic research among ethnically and linguistically diverse populations in all settings.

Linking principles to practices at the ground level is the most powerful way to ensure that valid consent is indeed realized. In this paper we have highlighted a number of key areas of practice and policy relating to the achievement and understanding of valid consent in genomic epidemiology in developing countries. In turn, these have suggested a number of areas of practice in which embedded ethico-social research would be of great value. These include: research into models of community consent and education for genomic epidemiology; the development of models for embedded empirical research on obtaining valid consent; research into the ethical and social factors important in building trust between communities and researchers; and research into the use of broad consent and the secondary research use of data and archived samples.

Informed consent is essential for research involving human subjects. However, little is known about whether researchers manage to communicate to potential study participants the required information as outlined in the Helsinki Declaration. The potential participants in a developing country may be illiterate and may have limited experience with medical care and research. The researchers’ communication skills are particularly important in such situations. Only a few empirical studies have addressed this issue.

Professor Dame Margaret Turner-Warwick made the suggestion that, for treatments such as surgery where damage could potentially result, the term “informed request” should be used rather than “informed consent”. The patient is, in effect, requesting treatment and this way of putting it might put the relationship between doctor and patient on a more trusting basis. Baroness O’Neill said this raised the issue of whether different rituals or procedures of consent should be used according to the context that is, according to the level of risk. The risks involved, and therefore information required by the patient, are very different when taking a blood sample, when compared with having surgery, taking part in a clinical trial or having your data used in medical research. Her opinion was that it was not a good idea to impose uniform procedures on how to inform the patient such as a mandatory form that needed to be filled in to prove consent was given only after the patient had been given all the relevant facts. It also raised the question of how much information a patient required to be considered “informed”. In her opinion, the amount and level of information given should be dictated by the patient, donor, or research subject, not by the physician. And it would be ethically wrong to require patients to handle a form as complicated as a mortgage application at a difficult time in their lives. Not all patients want to be burdened with all the detail, while other require an in depth understanding. She emphasized that there are two parts to the issue of informed consent: the information given and the consent of the patient. The information available at a particular time influences a patient’s decision. In an ideal world, if patients can make a choice, then they should be able to rescind that decision.
Most of the participants signed informed consent forms and a vast majority felt that they received enough information before deciding to participate. On the contrary, several were not aware that they could voluntarily withdraw their participation. Participants in observational studies were more likely than those in clinical trials to perceive that refusal to participate in the parent study would affect their regular medical care.18

All the factors involved in the decision-making process described may enhance participant’s ability to exercise their autonomy and their right to choose. They may also assure research institutions that they are conducting the trials without exercising any type of coercion over the participants. Therefore, it is relevant for every research setting to design strategies to ensure the confluence of volunteers’ and researchers’ interests in a harmonic and equitable way.19

These conclusions are bound to be resisted or simply dismissed. They do propose a highly regulated, and possibly unrealistic, exchange of information, and will surely be rejected by hard core scientists, paternalistic physicians, and interested third parties. Nevertheless subjects and patients must be protected, because it is perverse for biomedical practice to support regressive attitudes toward safeguarding the weak and defending the autonomy of individuals. It is also worrying to observe how bioethics is becoming ever more sympathetic to the interests of the strong and the mighty, offering arguments that favour sponsor countries, research institutions, biomedical big business, and career minded investigators. Patients and research subjects must continue to be the main concern of ethics, taking care to eliminate any and all weaknesses and deficiencies from the process of providing complete and pertinent information to ensure protection of the vulnerable and unfailing respect for their autonomy.20

The QuIC is a brief, reliable, and valid questionnaire that holds promise as a standardized way to assess the outcome of the informed consent process in cancer clinical trials.21

**CONCLUSION:** Many accounts of informed consent in medical ethics claim that it is valuable because it supports individual autonomy. Unfortunately there are many distinct conceptions of individual autonomy, and their ethical importance varies. A better reason for taking informed consent seriously is that it provides assurance that patients and others are neither deceived nor coerced. Present debates about the relative importance of generic and specific consent (particularly in the use of human tissues for research and in secondary studies) do not address this issue squarely. Consent is a propositional attitude, so intransitive: complete, wholly specific consent is an illusion. Since the point of consent procedures is to limit deception and coercion, they should be designed to give patients and others control over the amount of information they receive and opportunity to rescind consent already given.

**REFERENCES**

3. BMRC Ethical guideline

4. Case IRB Guidebook


