Abstract 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.

The emphasis in most externally sponsored research projects in developing countries is on laborious documentation of several mechanical aspects of the research process rather than on assuring true comprehension and voluntary participation. The onus for the oversight of this process is often left to overworked and ill-equipped local ethics review committees. Current guidelines and processes for obtaining informed consent should be reviewed with the specific aim of developing culturally appropriate methods of sharing information about the research project and obtaining and documenting consent that is truly informed. Further research is needed to examine the validity and user friendliness of innovations in information sharing procedures for obtaining consent in different cultural settings.

Keywords Informed consent; Biomedical research/ethics; Ethics committees, Research; Human experimentation/ethics; Bioethical issues; Codes of ethics; Guidelines; Review literature; Developing countries (source: MeSH, NLM).

Introduction

Informed consent is the cornerstone of the ethical conduct and regulation of research, and it has been a focus of attention in guidelines for conducting research and the ethical oversight of research. It is not the purpose of this article to review the entire landscape of ethical issues in international research in developing countries because these issues are diverse and include issues such as standards of care, prior agreements on assured benefits, use of placebo treatments and the relevance of research to local priorities. Instead this paper focuses on the issue of informed consent in order to review the relevant progress in this field in recent years and highlight some issues of relevance to developing countries.

Although general medical practice has been guided by ethical principles for centuries, the history of human medical experimentation is notable for the relative paucity of universally agreed guidelines or a framework for the ethical conduct of research. The basic principles of ethics in medical practice stem from the Hippocratic code of conduct which specifies that “the physician will use treatment to help the sick according to his ability and judgment, but never with the view to injury and wrongdoing” (1). For centuries medical practice and conduct largely relied on the physician’s attributes of compassion and understanding and the acceptance of the principle of primum non nocere (1). It was Claude Bernard who at the turn of the 20th century first highlighted the importance of human experimentation and the principle of medical and surgical morality that consisted of “never performing on man an experiment which might be harmful to him in any extent even though the results might be highly advantageous to science, i.e. to the health of others” (2).

The code of conduct during human medical experimentation was, however, largely left to the discretion of researchers and concerned individuals, and few believed that regulation was necessary. The Second World War changed all that. The atrocities committed by the Nazis and by Japanese forces on prisoners and civilians in Europe and Asia shocked the world and led to the Nuremberg trials and the subsequent Nuremberg code. Not surprisingly, the Nuremberg code largely dealt with issues of consent and competence in giving consent to participate in medical research or experimentation (3).

Despite the heightened awareness of the need for safeguards and guidelines for human experimentation, it is debatable whether the Nuremberg declaration made a significant difference to the actual practice and conduct of medical research. Some notable scandals, such as the Tuskegee syphilis study in the United States of America (4) and the landmark publication

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by Beecher (5) on the ethical irregularities that occurred in at least 22 medical research projects in the United States, changed all this. Beecher reviewed various aspects of trial design, consent processes and the conduct of research projects. While Beecher highlighted various ethical issues and requirements in this seminal piece, he concluded by maintaining that “…the more reliable safeguard was provided by the presence of an intelligent, informed, conscientious, compassionate, responsible investigator” (5). The first international move towards developing guidelines for the ethical regulation of research was the 1964 Declaration of Helsinki made by the World Medical Association (6) and the subsequent development of guidelines by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (7). These two sets of guidelines are widely regarded as coming closest to consensus-driven international guidelines for the ethical conduct of research.

In recent years widespread disquiet and controversy surrounding the trials of antiretroviral drugs in Africa (8, 9) have led to a reconsideration of several aspects of internationally sponsored research. The consequent debate highlighted the lack of clarity in various regulations and led to a review of the ethical regulation of research, especially in the areas of informed consent, standards of care and issues of the responsibility of investigators. The Helsinki declaration was revised in 2000 and the CIOMS guidelines were revised in 2002. These have been supplemented with other national guidelines. Additionally, there have been recent reviews of the ethical conduct and regulation of internationally sponsored research in developing countries by several agencies involved in the oversight of these processes in the United States (10), the United Kingdom (11) and in Europe (12). Some maintain that these guidelines may politicize and threaten the work of research ethics committees (13).

Methods
The fundamental underpinning of ethical medical research is the requirement to obtain informed consent for voluntary participation. While these issues have been seemingly addressed within developed countries, problems still occur (14). In particular, there is disquiet about the way these issues are tackled in guidelines and policy documents, especially in the context of sponsored research within developing countries.

In order to understand the context of the debate around informed consent, I undertook an empirical analysis of all available international guidelines. In addition, relevant electronic databases were searched for literature on informed consent for health research in developing countries. These databases searched were Medline, PubMed, ExtraMed, EMBASE, and POPLINE. A standardized set of questions exploring developments in the process of obtaining informed consent, areas of controversy and potential solutions was sent to 28 leaders in international research ethics. Of these 19 (68%) responded, and some of their views are incorporated in this paper.

Essential elements of informed consent
There are several key elements of the consent process that require information to be shared by the research team with the potential participant in a manner that can be adequately grasped and acted upon. Fig. 1 shows a conceptual framework for the elements and determinants of the process of developing informed consent.

During the first step, the research team provides full and transparent information about the research and participants’ rights in a manner that can be understood by the potential participants. Other aspects of the research project, especially the nature of sponsorship, the benefits of participation, and the responsibility for care and complications, must be carefully explained to participants. In particular, they must be given the opportunity to question the research team in order to clear up ambiguities and obtain additional information.

The second step is critically important: the participant must understand what is being asked of him or her. This can truly occur only if the information is presented in a manner that is simple yet conveys the key elements of the proposed research. Although this is a difficult step, it is crucial that this interaction occurs when the potential participant is in a calm frame of mind. Participants may have a different understanding of the research depending on how much time is spent explaining it, their opportunities to interact with the research team and their literacy levels. Illiteracy, however, must never be taken to mean that a potential participant is unable to comprehend complex information, but it does mean that the information may need to be presented differently.

The next step in the process is that the potential participant must freely agree to take part in the research. Therefore, not only must the participant understand the project but he or she must also be competent to give his or her consent.

Despite the difficulties in implementing these steps among those who are illiterate, standard procedures require that this consent be given in writing.

Current guidelines and controversies
All guidelines for health research regard the process of obtaining informed consent as a fundamental prerequisite for conducting research. Table 1 summarizes the requirements of guidelines on informed consent (6, 7, 10–12).

Box 1 lists several areas in which there is lack of clarity with regard to the consent process and its application to population-based research in developing countries. In general, the broad areas where there are problems are discussed below.
Informed consent versus “understood consent”

Although most guidelines emphasize the importance of obtaining informed consent and the practical steps needed to document it, there is little emphasis on participants’ understanding of the project. None of the processes involved in administering and recording the consent process evaluate the potential participant’s true understanding of the nature and implications of the research process. Even among literate research participants in the developed world, and despite the use of varied procedures and means of communication, there may be a relatively poor understanding of the nature of the research (15, 16). The evaluation of a gynaecological research trial in Sweden found that a significant number of participants thought that the research procedures were part of their routine care (17).

This issue becomes especially important among illiterate and disenfranchised populations, where full disclosure of relevant information must be done in a way that allows potential participants to understand the nature of the project and the

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**Table 1. Comparison of global guidelines on informed consent**

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<td>In any research on human beings, each potential participant must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest and institutional affiliations of the researchers, the anticipated benefits and potential risks of the research and the discomfort that participation may entail.</td>
<td>Researchers should develop culturally appropriate ways of disclosing the information necessary for adherence to the substantive ethical standards of informed consent, paying particular attention to disclosures relating to diagnosis and risk, research design and possible post-trial benefits to the participants.</td>
<td>Verbal consent is acceptable only if written consent is inappropriate.</td>
<td>In all biomedical research involving humans the investigator must obtain the voluntary informed consent of the potential participant or in the case of an individual who is not capable of giving informed consent, the permission of a legally authorized representative in accordance with applicable law. The use of a waiver of informed consent is regarded as uncommon and exceptional, and must in all cases be approved by an ethical review committee.</td>
<td>The consent of a family or community leader may be required in addition to obtaining an individual’s consent.</td>
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<td>The physician should then obtain the potential participant’s freely given informed consent, preferably in writing. If the consent cannot be obtained in writing, consent must still be formally documented and witnessed.</td>
<td>Procedures must be developed and described in such a way to ensure that potential participants understand the information provided in the consent process.</td>
<td>The council also recommends adopting the concept of “genuine consent” as opposed to “informed consent”.</td>
<td>Written consent is preferable.</td>
<td>Verbal consent is appropriate only if the participant is illiterate.</td>
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<td>When a potential participant is dependent on a caregiver, informed consent should be obtained by a well informed physician who is not engaged in the investigation and who is completely independent of this relationship.</td>
<td>While the permission of a community representative may be sought before researchers approach potential participants, in no case may such permission replace the requirement of obtaining a competent individual’s informed consent, without coercion or inducement.</td>
<td>Community consent is required when appropriate.</td>
<td>Community consent is the consent</td>
<td>These guidelines provide a checklist of eight essential aspects of research that should be addressed during the consent process.</td>
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<td>In cases in which the potential participant is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the participant’s legally authorized representative in accordance with applicable law.</td>
<td>Researchers working in developing countries should indicate in their research protocols how they will minimize the likelihood that potential participants will mistakenly believe that the purpose of the research is solely to administer treatment rather than to contribute to scientific knowledge.</td>
<td>Multiple forms of consent are acceptable. In the case of research posing minimal risks, participants may waive consent.</td>
<td>Guideline 5 lists 26 essential aspects of research that must be addressed during the consent process.</td>
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* Adapted from reference 20.
and agreement to participate. Informed consent for research, the associated risks and benefits, and agreement to participate will make the process unwieldy. 

1. The focus is largely on written documentation rather than on ensuring that potential participants understand the entire research process.
2. The written documentation process and the language used is often complex and stems primarily from a desire to provide legal protection to researchers and sponsors of the research rather than to provide information to participants.
3. The information required under various items in the informed consent process, such as sponsorships, funding, assured benefits, and risks, is excessive, and lengthy consent forms are often mistrusted by communities.
4. There is little agreement on the best means of providing information to ensure that the community and potential participants truly understand the nature of the research and the possible risks and benefits.
5. The exact balance of consent (communal, family and/or individual) needed in traditional societies is uncertain.
6. In case of illiterate populations, alternative methods of obtaining consent, such as recorded or witnessed consent using third parties or community representatives, are rarely used.

Current documents on information disclosure in many sponsored research projects are dictated by the regulations of the ethics committees of sponsoring institutions. The informed consent forms are also usually designed in developed countries, translated and then back-translated to ensure that they retain their original meaning. This emphasis on literal translation serves largely to satisfy the legality of the process rather than the information and comprehension needs of the community or individuals who may potentially participate in research.

Community consent versus individual consent

All guidelines emphasize the importance of obtaining consent from individuals who may be participants in the actual research, but they differ greatly in defining the role of community leaders or gatekeepers. There has been a growing appreciation of the importance of community leaders and families in the context of decision-making. While the process of going through such community gatekeepers does not take away from the importance of the individual’s understanding of and willingness to participate in the research, it adds an element of security in traditional societies where communal consciousness and living is the norm. While it is recognized that these multiple levels of consent within communities require community information and discussion, in many developing countries this process is poorly defined. It must also be underscored that although it is helpful, this stepwise process of information sharing and consent can be resource intensive, labour intensive and time intensive.

Consent on complex issues

With the growing importance of genetic research and the expansion of such projects to developing countries, the specific nature of the consent process for this kind of research has become important. The consent process for participation in genetic research may be difficult even for relatively educated individuals to understand, and certainly explaining the complex processes of genetic research and the potential long-term implications and risks to largely illiterate populations is challenging. These difficulties may increase the risk that exploitation will occur during genetic research projects undertaken in developing countries.

Since the completion of the human genome project, much of the research on drug development and clinical efficacy has taken genetic polymorphisms into account; this requires access to large genetic databases, and the developing world is a natural target for such research. It is interesting to contrast the information and consent processes used in different countries. For example, in Iceland where the entire genetic database of the population has been made available, the process of consent includes public consultation and debate, and individuals may opt out of sharing their genetic information (22, 23). However, no such discussion took place in Tonga where the government initially gave its consent to share the population’s genetic data, but later had to retract it after public outcry (24, 25). Other studies on genetics and infectious diseases that are under way in Africa, such as the HapMap project (26), have adopted processes whereby local ethics committees play a primary role in overseeing the process of providing information and obtaining consent. These approaches are relatively new, and it is imperative that the informed consent processes and outcomes of genetic research remain under scrutiny. For example, recent findings from Sweden indicated that many patients voluntarily
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Given the problems in the process, how can we make improvements in the informed consent process to ensure that participation in research is truly voluntary and is based on a full understanding of the proposed research and the individual’s rights? This may only be possible in an environment where human rights are respected and the fundamental principles of justice govern the design and conduct of research. While the role of a caring and compassionate researcher is fundamental to conducting appropriate research in developing countries, the following permutations of the process and regulations may make it both easier and more ethical.

Changing the focus of informed consent

It may help to change the focus from obtaining informed consent to providing adequate information about the project and ensuring that potential participants clearly understand the project. This would ensure that potential participants adequately understand the exact nature of the research and its outcomes and procedures; it would help minimize the “therapeutic misconception” (36). This may require a series of iterative processes, ranging from conducting community information sessions to providing information that participants can refer to when needed. For example, information about the nature and implications of the research could be provided as an appropriately worded and illustrated information sheet. To ensure comprehension, researchers could use a questionnaire or interview the potential participant after they have received the information and before consent is obtained. A staged process for obtaining consent has also been used in special circumstances (37) such as the treatment of childhood leukaemia, and should be used more commonly.

Using innovative materials and processes

Another path to take would be to use innovative materials and processes to ensure that individuals or community members have an adequate understanding of the research. This may consist of using information, education and communication materials, descriptive videos or illustrations. There is sufficient information from the health education sector to indicate that comprehension, and indeed retention of concepts, can be greatly enhanced by using these techniques. Indeed among populations with low levels of literacy this may be the only option. For example, using a “flower diagram” to explain risks and benefits during an interactive session, has been found to be useful in social science research (21).

Using alternative processes for documentation

While a written and witnessed process for documenting informed consent remains the norm, alternative processes that are more user-friendly and can be verified, must be considered. These include variations on the process of obtaining verbal consent (individual or communal) and the use of techniques such as revisits or reinterviews at a later stage or making an audio recording of consent. Many individuals in developing countries are wary of voluminous and complex consent forms because they are perceived as carrying other legal risks. Alternative methods for documenting consent, such as witnessed consent, may be more acceptable to the community. Similarly, using the improved technology of video and audio recordings during the consent process may carry the dual benefits of documenting consent as well as acting as a mechanism for oversight by ethics review committees. However, these alternative processes must be overseen and monitored, and their effectiveness must be assessed before they can be recommended.

Involving senior staff and communication experts

In most community-based research projects the consent process is overseen by relatively junior field staff or community workers. This process must be given the importance it deserves and should be overseen by senior research staff. It should also involve communication experts specifically designated to work on the consent process. Teams of researchers and communication experts working together can greatly increase the validity and usefulness of the process. Other processes to consider include using an ombudsman to monitor the process or a third party to mediate. These recommendations may have resource implications, but this is a minor issue given the fundamental importance of ensuring truly voluntary and informed participation in research.
Conclusions
Obtaining truly informed and culturally relevant consent is fundamental to the ethical conduct of research and is of particular importance in developing countries. The assessment and monitoring of the process of informed consent is also an essential part of the research process and is a joint responsibility of the local ethics review committee and the sponsors of research. However, the fundamental process of designing and implementing an appropriate process for providing information and obtaining consent requires a knowledgeable and sympathetic researcher who has a full understanding of the issues. While ethics review committees can help in oversight, only an active and transparent partnership between research sponsors, investigators and the community can make this happen.

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Résumé
Au-delà du consentement éclairé
Bien que son introduction soit relativement récente, le consentement éclairé joue un rôle central dans la réglementation et la conduite éthiques des recherches sur l’homme. Cependant, les procédures recommandées par les directives pour l’obtention du consentement éclairé (habituellement un consentement écrit) sont souvent difficiles à mettre en œuvre dans les pays en développement. Le présent article examine ces directives et passe en revue les points de vue les plus répandus sur les controverses, les ambiguïtés et les problèmes qu’elles soulèvent, ainsi que les solutions potentielles.

Dans la plupart des projets de recherche menés dans les pays en développement avec des subventions extérieures, l’accent est mis sur une documentation laborieuse de plusieurs aspects mécaniques du processus de recherche, plutôt que sur les efforts pour garantir une compréhension véritable et une participation volontaire. La charge de la surveillance de ce processus est souvent laissée à des comités d’éthique locaux surchargés de travail et mal équipés. Il convient de réexaminer les directives et les procédés actuallement appliqués pour obtenir le consentement éclairé dans l’objectif spécifique de mettre au point des méthodes appropriées sur le plan culturel pour faire part des informations sur le projet de recherche et pour obtenir et documenter un consentement qui soit véritablement éclairé. Des travaux de recherche supplémentaires sont nécessaires pour examiner la validité et la convivialité des innovations apportées aux procédures de communication des informations en vue d’obtenir un consentement éclairé dans différents contextes culturels.

Resumen
Más allá del consentimiento informado
Aunque se trata de un requisito relativamente reciente, la función del consentimiento informado en las investigaciones con seres humanos es fundamental para su regulación y realización éticas. Sin embargo, los procedimientos que suelen recomendar las directrices en la materia para obtener el consentimiento informado (generalmente escrito) son difíciles de llevar a la práctica en los países en desarrollo. En este artículo se examinan las normas existentes para obtener el consentimiento informado, así como las opiniones más barajadas en las polémicas, las ambigüedades y las dificultades planteadas por esas normas, y se sugieren posibles soluciones.

La mayoría de los proyectos de investigación patrocinados externamente en los países en desarrollo hacen hincapié en una documentación laboriosa de varios aspectos mecánicos del proceso de investigación, más que en garantizar una verdadera comprensión del hecho y la participación voluntaria. La responsabilidad de supervisar este proceso se suele delegar en unos comités de ética locales desbordados de trabajo y mal pertrechados. Las normas y los procedimientos empleados actualmente para obtener el consentimiento informado deberían modificarse con el objetivo específico de desarrollar métodos culturalmente idóneos para compartir la información acerca del proyecto de investigación y para obtener y documentar un consentimiento efectivamente informado. Es necesario emprender nuevas investigaciones que determinen la validez y la facilidad de uso de las novedades introducidas en los procedimientos de intercambio de información para obtener el consentimiento en diferentes entornos culturales.
References


Box 2. Text of Guideline 5 of the International ethical guidelines for biomedical research involving human subjects (7).

Obtaining informed consent: essential information for prospective research subjects

Before requesting an individual’s consent to participate in research, the investigator must provide the following information, in language or another form of communication that the individual can understand:

1. that the individual is invited to participate in research, the reasons for considering the individual suitable for the research, and that participation is voluntary;
2. 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;
3. 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;
4. for controlled trials, an explanation of features of the research design (e.g., randomization, double-blinding), and that the subject will not be told of the assigned treatment until the study has been completed and the blind has been broken;
5. 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;
6. whether money or other forms of material goods will be provided in return for the individual’s participation and, if so, the kind and amount;
7. that, after the completion of the study, subjects will be informed of the findings of the research in general, and individual subjects will be informed of any finding that relates to their particular health status;
8. that subjects have the right of access to their data on demand, even if these data lack immediate clinical utility (unless the ethical review committee has approved temporary or permanent non-disclosure of data, in which case the subject should be informed of, and given, the reasons for such non-disclosure);
9. 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;
10. the direct benefits, if any, expected to result to subjects from participating in the research;
11. the expected benefits of the research to the community or to society at large, or contributions to scientific knowledge;
12. whether, when and how any products or interventions proven by the research to be safe and effective will be made available to subjects after they have completed their participation in the research, and whether they will be expected to pay for them;
13. any currently available alternative interventions or courses of treatment;
14. the provisions that will be made to ensure respect for the privacy of subjects and for the confidentiality of records in which subjects are identified;
15. the limits, legal or other, to the investigators’ ability to safeguard confidentiality, and the possible consequences of breaches of confidentiality;
16. policy with regard to the use of results of genetic tests and familial genetic information, and the precautions in place to prevent disclosure of the results of a subject’s genetic tests to immediate family relatives or to others (e.g., insurance companies or employers) without the consent of the subject;
17. the sponsors of the research, the institutional affiliation of the investigators, and the nature and sources of funding for the research;
18. the possible research uses, direct or secondary, of the subject’s medical records and of biological specimens taken in the course of clinical care (see also Guidelines 4 and 18 Commentaries);
19. whether it is planned that biological specimens collected in the research will be destroyed at its conclusion, and, if not, details about their storage (where, how, for how long, and final disposition) and possible future use, and that subjects have the right to decide about such future use, to refuse storage, and to have the material destroyed (see Guideline 4 Commentary);
20. whether commercial products may be developed from biological specimens, and whether the participant will receive monetary or other benefits from the development of such products;
21. whether the investigator is serving only as an investigator or as both investigator and the subject’s physician;
22. the extent of the investigator’s responsibility to provide medical services to the participant;
23. that treatment will be provided free of charge for specified types of research-related injury or for complications associated with the research, the nature and duration of such care, the name of the organization or individual that will provide the treatment, and whether there is any uncertainty regarding funding of such treatment.
24. in what way, and by what organization, the subject or the subject’s family or dependants will be compensated for disability or death resulting from such injury (or, when indicated, that there are no plans to provide such compensation);
25. whether or not, in the country in which the prospective subject is invited to participate in research, the right to compensation is legally guaranteed;
26. that an ethical review committee has approved or cleared the research protocol.