

## 5. RESEARCH REQUIRING ADDITIONAL ATTENTION

South African research ethics committees must pay special attention to protecting the welfare of certain classes of participants,<sup>6</sup> such as minors (this includes children and adolescents), pregnant women, prisoners, people with intellectual or mental impairment, people for whom English is not a first language, and people from vulnerable communities. Certain types of research also require special attention. Research ethics committees may impose additional measures to protect the welfare of participants. Research ethics committees may make it mandatory to conduct post-research investigations to review whether there was compliance with the additional measures imposed. If compliance was defective, research ethics committees may withdraw approval for the research investigation concerned.

Participants whose involvement needs additional attention include:

- Minors – children and adolescents
- Persons with intellectual or mental impairment
- Disabled persons
- Persons in dependent relationships
- Persons participating in research as groups (referred to as collectivities)
- Pregnant women

Types of research that need additional attention include:

- Research involving indigenous medical systems
- Emergency care research
- Innovative therapy or interventions
- Research necessitating ambiguity of information for participants.

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<sup>6</sup> For further, more detailed, discussion on special classes of participants, refer to CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002) Guidelines 13-17, [http://www.cioms.ch/guidelines\\_nov\\_2002\\_blurb.htm](http://www.cioms.ch/guidelines_nov_2002_blurb.htm) [last visited 15 October 2004]; US Department of Health & Human Services, Office for Human Research Protections, <http://www.hhs.gov/ohrp/> [last visited 15 October 2004].

## 5.1 Research involving minors

Minors<sup>7</sup> should participate in research only where their participation is indispensable to the research and where participation is not contrary to the individual minor's best interests.<sup>7</sup> The research should investigate a problem of relevance to children. Where research involving minors is proposed, a research ethics committee should determine whether the research might be equally informative if carried out with consenting adults. If so, the research ethics committee should require strong justification for the inclusion of minors. Note that all types of **clinical research on minors** should be scrutinized carefully.

For purposes of these guidelines,

- 'Child' means a person who has not yet reached puberty;
- 'Adolescent' means a person who has reached puberty;
- 'Therapeutic' means interventions that may hold out the prospect of direct health-related benefit for the participant;
- 'Non-therapeutic' means interventions that will not hold out the prospect of direct health-related benefit for the participant but results may be produced that significantly contribute to generalisable knowledge about the participant's condition.

## 5.2 Research involving a child

Research involving a child should be approved only if:

- The research, including observational research,<sup>8</sup> places the child at no more than minimal risk (that is, the risk commensurate with daily life or routine medical or psychological examinations – referred to as 'negligible risk' in some guidelines); or
- The research involves more than minimal risk but provides possible benefit for the child participant. The degree of risk must be justified by the potential benefit; or
- The research, including observational research,<sup>9</sup> involves greater than minimal risk, with no prospect of direct benefit to the child participant, but has a high probability of providing significantly generalisable knowledge; that is the risk should be justified by the risk-knowledge ratio. The risks must represent no more than a minor increase over minimal risk.

Consent for minors to participate in research must be obtained from:

- The parents or legal guardian in all but exceptional circumstances (such as emergencies); and
- The minor where s/he is competent to make the decision; and
- Any organization or person required by law, eg the National Health Act 61 of 2003.
- Where the minor is not competent, assent from the child (where appropriate) and permission from the parent(s) or legal guardian must be sought. No other caregiver can act on behalf of a child in providing consent to participate.
- A minor's refusal to participate in research must be respected, ie such refusal settles the matter.
- In all cases, the protocol must provide sufficient information to justify clearly why children should be included as participants.

### 5.2.1 Child assent:

<sup>7</sup> Section 6 of the Children's Bill stipulates various factors that must be considered when applying the best interest of child standard. Research ethics committees should familiarise themselves with these factors.

<sup>8</sup> Of a non-invasive nature that involves no interference with the bodily or psychological integrity of the child.

<sup>9</sup> Of an invasive nature that may involve interference with the bodily or psychological integrity of the child, eg questions about sensitive matters that could cause emotional upset for the child. The consequences of reporting obligations on health care workers in cases of suspected abuse must be taken into consideration too.

The research ethics committee must ensure that adequate steps are outlined in the protocol to obtain the child's assent when, in the judgement of the research ethics committee, the child is capable of providing such assent. When the research ethics committee decides that assent is required, it must also indicate whether and how such assent must be documented.

### 5.2.2 Parental permission:

Where the research does not involve greater than minimal risk to the child, or involves greater than minimal risk but presents the likelihood of direct benefit to the child, the research ethics committee may find that the permission of one parent is sufficient. Permission from both parents is necessary where the research involves greater than minimal risk, is of no direct benefit to the child but is likely to produce generalisable knowledge. Where only one parent is available for reasons including the death, incompetence or disappearance of the other, or where a court has placed the child in the sole custody of one parent, then the permission of that one parent is sufficient for participation in the latter type of research. In the event of conflicting views between the parents, the child's best interest settles the matter.<sup>10</sup>

## 5.3 Adolescents

In terms of section 39(4) of the Child Care Act 74 of 1983 and in the absence of specific legislative provisions to the contrary, adolescents who have attained the age of 14 years are legally capable of consenting to medical treatment of themselves and their children. Adolescents who have attained the age of 18 years are legally capable of consenting to surgical operations upon themselves provided in all cases the adolescent is competent, ie sane and sober. Conversely, the consent of a parent or legal guardian is required for medical treatment or an operation if the adolescent is under the age of 14 or 18 years respectively. Note, however, that an unmarried mother who is herself a minor may not consent to the participation of her child in research investigations. Her guardians (usually her parents) are also the guardians of her child<sup>11</sup> and must thus consent to the child's participation as set out above.

The Children's Bill will repeal the Child Care Act, amongst other legislation. The Children's Bill makes no provision for age categories and consent to treatment. Instead it states that '[e]very child capable of participating meaningfully in any matter concerning that child has the right to participate in those proceedings in an appropriate way and views expressed by the child must be given due consideration'.<sup>12</sup> The National Health Act does not distinguish between minors who are children and minors who are adolescents and requires the consent process to be the same for both groups, subject to the distinction between 'therapeutic' and 'non-therapeutic' research. As discussed above, research is not the same as medical treatment. It is rarely arguable that participation in medical research is necessary.

It is arguable, however, that adolescents may be capable of consenting themselves to certain types of research participation and that, for particular types of research, it may be desirable that they do so unassisted.

**5.3.1 Research involving adolescents who may consent unassisted** should be approved only if:

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<sup>10</sup> See n 3.

<sup>11</sup> In terms of the Guardianship Act 192 of 1993.

<sup>12</sup> Section 10 of the Children's Bill. Section 17 of the Bill stipulates the age of majority as 18 years.

- The research, including observational research,<sup>13</sup> places the adolescent at no more than minimal risk; **and**
- The nature of the research is such that, in the opinion of the research ethics committee, the parents or legal guardians or community at large are unlikely to object to the adolescent consenting him or herself to participation in the investigation. The opinion of the research ethics committee must be informed by information gathered from the community concerned and by contributions from the lay members of the committee.
- In all cases, the protocol must provide sufficient information to justify clearly why adolescents should be included as participants.
- In all cases, the protocol must justify clearly why the adolescent participants should consent unassisted.

**5.3.2** Research involving adolescents who assent assisted by parents or legal guardians should be approved only if:

- The research involves more than minimal risk but provides possible direct benefit for the adolescent participant. The degree of risk must be justified by the potential benefit; or
- The research, including observational research,<sup>14</sup> involves greater than minimal risk, with no prospect of direct benefit to the adolescent participant, but has a high probability of contributing to generalisable knowledge. In addition the risk must represent no more than minor increase over minimal risk. (See 5.2).
- In all cases the protocol must provide sufficient information to justify clearly why adolescents should be included as participants.
- In all cases, assent from the adolescent and permission from the parent(s) or legal guardian must be sought. No other caregiver can act on behalf of an adolescent in providing consent to participate.

**5.3.3** Adolescent assent: The research ethics committee must ensure that adequate steps are outlined in the protocol to obtain the adolescent's assent when, in the judgement of the research ethics committee, the adolescent is capable of providing such assent. When the research ethics committee decides that assent is required, it must also indicate whether and how such assent must be documented.

**5.3.4** Parental permission: Where, in the judgement of the research ethics committee, the adolescent should not consent unassisted, or where the research involves greater than minimal risk but presents the likelihood of direct benefit to the adolescent, the research ethics committee may find that the permission of one parent is sufficient. Permission from both parents is necessary where the research involves greater than minimal risk, is of no direct benefit to the adolescent but is likely to produce generalisable knowledge about the adolescent's condition. Exceptions would include situations as set out in 5.2.2.

## **5.4 Research involving persons in dependent relationships or comparable situations**

Persons whose proposed involvement in research arises from dependent or comparable relationships need additional attention and the research ethics committee must be satisfied that their consent is both adequately informed and voluntary.

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<sup>13</sup> Of a non-invasive nature that involves no interference with the bodily or psychological integrity of the adolescent.

<sup>14</sup> Of an invasive nature that may involve interference with the bodily or psychological integrity of the adolescent, eg questions about sensitive matters that could cause emotional upset for the adolescent. The consequences of the reporting obligations on health care workers in cases of suspected abuse must be taken into consideration too.

It is not possible to define such relationships exhaustively, but they include persons who are in junior or subordinate positions in hierarchically structured groups and may include relationships between:

- Older persons and their caregivers;
- Persons with chronic conditions or disabilities and their caregivers;
- Wards of State and guardians;
- Patients and health-care professionals;
- Students and teachers;
- Prisoners and prison authorities;
- Persons with life-threatening illnesses;
- Employees and employers, including farm workers and their employers, including members of the uniformed services and hospital laboratory staff and their employers.

### **5.5 Research involving women**

Exclusion of women as research participants has led to a lack of data needed to promote women's health. Research ethics committees should consider whether the exclusion of women is justified in terms of research priorities and the specific research question under consideration. As part of advocating improved health for women, researchers have ethical obligations to conduct research that does not perpetuate discriminations against women by unfairly or unjustifiably excluding them from study protocols.

Research ethics committees must give extra attention to research that involves women who are, or may become pregnant, because of the additional health concerns during pregnancy and the need to avoid unnecessary risk to the foetus. Reasons for excluding women from research should be adequately justified both from the point of protecting the health of a foetus and from the perspective of whether such exclusion is scientifically supportable.

Guidelines for inclusion of "special populations" as participants in research (The IRB Policy and Procedure Manual [1997])

No research activities involving pregnant women and foetuses may be undertaken unless:

- Appropriate studies on animals and non-pregnant individuals have been completed
- The purpose of the activity is to meet the health needs of the mother of the particular foetus, the risk to the foetus is minimal and, in all cases, presents the least possible risk for achieving the objectives of the activity.

Individuals engaged in the activity will have no part in:

- Any decision as to the timing, method and procedures used to terminate the pregnancy,
- Determining the viability of the foetus at the termination of the pregnancy.
- No procedural changes, which may cause greater than minimal risk to the foetus or the pregnant woman, will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity.

### **5.6 Pregnant women as participants.**

No pregnant woman may be involved as a participant in any research activity unless<sup>15</sup>:

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<sup>15</sup> Clinical trials involving pregnant women or nursing mothers should ideally involve products where the toxicology in adults is established and is acceptable. In the case of pregnant women the potential risks associated with using a substance whose short term and long term effects on a foetus and developing infant are unknown, should be outweighed by the benefits. An example of a positive risk benefit ratio would be the use of anti-retrovirals in mother to child HIV transmission studies. For nursing mothers, the amount of drug passing into breast milk should be established and the potential impact on a breast fed infant anticipated, and the mother so advised.

- The purpose of the activity is to meet the health needs of the mother and the foetus will be placed at risk only to the minimum extent necessary to meet such needs, or
- The risk to the foetus is minimal.

Any activity permitted above may be conducted only if the mother is legally competent and has given informed consent after having been fully informed about the possible impact on the foetus.

The father's informed consent need not be secured if:

- The purpose of the activity is to meet the health needs of the mother;
- His identity or whereabouts cannot reasonably be ascertained;
- He is not reasonably available; or
- The pregnancy resulted from rape.

### **5.7 Research involving foetuses**

No foetus in utero may be involved as a participant in any research activity unless:

- The purpose of the activity is to meet the health needs of the particular foetus and foetus will be placed at risk only to the minimum extent necessary to meet such needs, or
- The risk to the foetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

Any activity permitted above may be conducted only if the mother and father are legally competent and have given their informed consent.

The father's informed consent need not be secured if:

- His identity or whereabouts cannot reasonably be ascertained;
- He is not reasonably available;
- The pregnancy resulted from rape.

### **5.8 Research involving indigenous medical systems**

Researchers must respect the cultures and traditional values of all communities. Participants involved in research of indigenous medical systems must be accorded the same degree of respect and protection from harm as participants in scientific medical research. The research must be submitted for ethics review. Any substance that is used on participants must be subjected to stringent toxicology testing. Researchers should furnish proof of safety to the research ethics committee.

### **5.9 Emergency care research**

The benefits of emergency care research include improved effective treatment for life-threatening conditions and improving therapies for survival and quality of life. Research into emergency medical treatment needs to involve participants who are experiencing medical emergencies. There are circumstances in which it is not possible to obtain consent for inclusion in emergency care research. In these circumstances, participants are vulnerable.

Accordingly, ethics committee approval of such research should be granted only if the ethics committee is satisfied that the following criteria will be met:

- After a protocol has been presented by a researcher giving clear reasons to justify the initiation of the emergency care research without consent, a research ethics committee in a

hospital with an acute care facility may approve the research without consent provided it is satisfied that:

- Reasonable steps are being taken to ascertain the religious and cultural sensitivities of patients experiencing medical emergencies;
- The condition of the patient precludes the giving of consent;
- Inclusion in the trial is not contrary to the interests of the patient;
- The research is intended to be therapeutic and poses no more risk than is inherent to the patient's condition or would be caused by alternative methods of treatment;
- The patient and the patient's next of kin or legal representatives will be informed as soon as is reasonably possible of the patient's inclusion in the study and of the option to withdraw from the research project at any time;
- The patient will be informed, and consent obtained, once the patient has regained consciousness;
- The research is based on valid scientific hypotheses and offers a realistic possibility of benefit over standard care.

### **5.10 Research involving innovative therapy or intervention**

Research, which must be considered by a research ethics committee, includes the use of any innovative therapy or intervention that is being tested on one or more patients.

A research ethics committee must ensure that appropriate provision is made for the long-term care and observation of participants and for the maintenance and security of records, before commencing new therapeutic or innovative procedure.

### 5.11 Research involving prisoners

Ethical review must take cognisance of the impact of a prisoner's incarceration on their ability to make a voluntary decision, without coercion, on whether or not to participate in research.

In addition, when reviewing research involving prisoners, ethics committees must meet the following requirements:

- A majority of the research ethics committee, other than prison members, shall have no association with the prison(s) involved, apart from their membership of the research ethics committee.
- At least one member of the ethics committee shall be a prisoner, or a prisoners' representative with appropriate background and experience to serve in that capacity. Where a research project is reviewed by more than one ethics committee, only one research ethics committee need satisfy this requirement of a prisoners' representative.

Research studies in South Africa may involve prisoners as participants only where the research has been registered with the National Health Research Ethics Council, and where, in the opinion of the MCC and the relevant research ethics committee, the clinical trial involves:

- Study of the possible causes, effects, and processes of incarceration, and of criminal behaviour, provided that the study presents no more than minimal risk and no more than inconvenience to the participants;
- Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the participants;
- Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on diseases that may be more prevalent in prisons and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) only after appropriate experts have been consulted;
- Research on practices, both innovative and accepted, that have the intent and probability of improving the health or wellbeing of prisoners. Where some prisoners may be assigned to control groups that may not benefit from the research, the research may proceed only after appropriate experts have been consulted. Research that could be conducted on a population other than prisoners should not be permitted, unless cogent motivation is presented to the research ethics committee, and the committee is satisfied that the motivation does not represent exploitative research. Research ethics committees should take into consideration the extent to which research facilitates the empowerment of prisoners as a vulnerable group.

### 5.12 Research involving vulnerable communities

South Africa is home to a number of vulnerable communities.<sup>16</sup> Where factors relating to vulnerability are an aspect of the research, the researchers should demonstrate how they will seek to redress that vulnerability. Particular caution must be exercised before undertaking research involving participants in such communities, and ethics committees must ensure that:

- Persons in these communities will not ordinarily be involved in research that could be carried out in non-vulnerable communities;
- The research is relevant to the health needs and priorities of the community in which it is to be carried out;
- Research participants should know that they are taking part in research and this research should be carried out only with their consent. This requires that particular attention be paid to the content, languages and procedures used to obtain informed consent.

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<sup>16</sup> UNAIDS define vulnerable communities as having some or all of the following characteristics: Limited economic development; Inadequate protection of human rights and discrimination on the basis of the health status; Inadequate community/cultural experience with the understanding of scientific research; Limited availability of health care and treatment options; Limited ability of individuals in the community to provide informed consent.

The research protocol should not adversely affect the routine treatment of patients, nor should it disrupt routine management protocols.

### 5.13 Research involving collectivities

A collectivity is an expression used to distinguish some distinct groups from informal communities, commercial or social groups.

Collectivities are groups distinguished by:

- Common beliefs, values, social structures and other features that identify them as a separate group;
- Customary collective decision-making according to tradition and beliefs;
- The custom of leaders expressing a collective view;
- Members of the collectivity being aware of common activities and common interests.

Researchers must seek research ethics committee approval for research involving a collectivity when any of the following conditions apply:

- Property or information private to the group as a whole is studied or used;
- The research requires the permission of people occupying positions of authority, whether formal or informal, or involves the participation of members acknowledged as representatives.
- Arrangements to address these issues should follow a process of respectful negotiation, and may include:
- The manner in which anticipated or actual disagreements between the researcher and the collectivity will be resolved;
- The seeking of informed consent from both the collectivity and individual participants;
- Resolution of the ownership of data and the rights of publication of research findings;
- The fair distribution of direct benefits and harms of the research among affected participants.

Research ethics committees should require that researchers provide a plan for consultation of community representatives, community involvement and feedback of results.

### 5.14 Research involving persons highly dependent on medical care

The involvement in research of participants who are highly dependent on medical care raises ethical issues that deserve special attention. The gravity of their medical condition may require invasive measures carrying increased risk. Researchers need to acknowledge that informed consent may be compromised by the effect of the medical condition on the participant's capacity to form an opinion or to communicate. Additionally, there may be a perception of coercion if a participant is reluctant to refuse consent for fear that it may compromise his or her medical treatment. Researchers need to consider whether an unfair burden of participation is being placed on groups such as those referred to below.

- **Emergency care research (see 5.9)**

The distinguishing features of emergency care research is that consent to commence a project usually has to be obtained rapidly, when the vulnerability of patients and families is likely to be greatest. Because of their extreme vulnerability, such persons should be excluded from all but minimally invasive observational research. Moreover, the circumstances surrounding emergency care research are such that it may not always be possible to obtain consent for inclusion without delaying the initiation of treatment, and so risking a reduction of potential benefits.

- **Intensive care research**

Characteristic features of intensive care research are the difficulties in communicating with patients receiving ventilatory assistance and the impairment of cognition in heavily sedated individuals.

Whenever possible, information regarding intensive care research should be obtained from potential participants before their admission to that care. Because of their extreme vulnerability such persons should be excluded from all but minimally invasive observational research.

- **Neonatal intensive care research**

Research involving infants receiving neonatal intensive care should be conducted in strict accordance with the principles set out in Research Involving Children (see 5.1) These principles do not permit research that is contrary to the child's best interests.

The small size and vulnerability of some infants are unique features of this research, which renders all but minimal intrusion likely to be contrary to the child's best interests. The collection of even small blood samples additional to those required for diagnostic purposes, or the handling of a low birth-weight infant to make observations, will demand careful scrutiny.

- **Terminal care research**

Research in terminal care is distinguished by the short remaining life expectancy of participants and potential vulnerability to unrealistic expectations of benefits.

Researchers must take care that the prospect of benefit from research participation is neither exaggerated nor used to justify a higher risk than that involved in the patient's current treatment.

Researchers must respect the needs and wishes of participants to spend time as they choose, particularly with family members

- **Research involving persons with impaired capacity to communicate**

The distinguishing features of research involving persons with impaired capacity to communicate includes acute impairment states requiring medical care, as well as non-acute states. In the former, the condition and medical care may mask the person's degree of cognition and require different means of expression. In the latter, the condition may be such as to prevent the person expressing wishes at all.

- **Research involving unconscious persons**

The distinguishing feature of research with unconscious persons is that, because of their incapacity for cognition or communication, it is impossible for them to be informed about the research or for a researcher to determine their wishes about it. Consent to participation in research by an unconscious person must be given by others, including relevant statutory authorities, on that person's behalf. Because of their extreme vulnerability unconscious persons should be excluded from all but minimally invasive observational research.

- **Human Research Ethics Committee consideration of research proposals involving persons highly dependent on medical care**

When research procedure precludes conformity to the principle of consent, and neither the prospective participant nor the participant's representative is able to give consent in advance, a research ethics committee may approve a research project without prior consent if it is satisfied that:

- Inclusion in the research project is not contrary to the interest of the patient;
- The research is intended to be therapeutic and the research intervention poses no more of a risk than that inherent in the patient's condition and alternative methods of treatment;
- The research is based on valid scientific hypotheses which support a reasonable possibility of benefit over standard care;

- As soon as reasonably possible, the participant and the participant's relatives or legal representatives will be informed of the participant's inclusion in the research, and will be advised of their right to withdraw from the research without any reduction in quality of care.

In the case of research proposals in which it is practicable to obtain consent before including in the research a participant who is highly dependent on medical care, an Ethics Committee must be satisfied that:

- Adequate provision will be made for informing patients and their relatives about the research, to ensure that stress and other emotional factors do not impair their understanding of it;
- The dependency of patients and their relatives on the medical personnel providing treatment does not affect any decision to participate.

### **5.15 Other special groups**

The discussion on special groups should not be limited to those already mentioned. Other special groups include: traumatised and comatose patients, terminally ill patients, elderly or aged patients, minorities, students, and employees. Research ethics committees must ensure special consideration is given to all these groups, especially with regard to informed consent. For a more detailed discussion on informed consent please refer to Section 2.6 of this document.