Informed consent for anaesthesiological and intensive care unit research: a South African perspective

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Abstract

Health research is highly regulated and controlled. The South African legal framework consists of the Bill of Rights, the National Health Act, and two sets of Department of Health guidelines, Medical Research Council Ethical Guidelines Book 1, and South African Health Professions Council General Ethical Guidelines for Health Researchers (Booklet 6) add an ethical overlay to the care and protection of research participants. These acts, regulations and guidelines are based on accepted international ethical guidelines and principles.

This article notes the historical background to the development of these guidelines, evaluates the South African Acts/regulations/guidelines as they pertain to anaesthesia and ICU research, and discusses attendant difficulties and pitfalls with reference to informed consent in this context. There are general requirements for participants' consent and health research ethics oversight, but a waiver of individual consent is possible under certain circumstances.

The regulations/guidelines restrict ICU research on temporary incompetent patients to minimal risk therapeutic research. Yet, there is increasing need for fundamental clinical ICU research which falls outside this limitation. Health research ethics committees (HRECs) generally apply their minds and may allow surrogate decision making (i.e. consent by a person other that the participant), but this can also be problematic since relatives may not know what the participant may have wanted, may object to the added responsibility of providing consent for research on top of consent for clinical treatment, and other surrogates may be subject to conflicts of interest. The regulatory framework should be brought into line with the requirements of the real world, international trends and practices.

Section 71 of the NHA was recently promulgated. If applied, it would mandate informed consent in all health research, disallowing surrogate consent and waivers of consent, and would halt almost all research on children since ministerial approval would be required for all non-therapeutic research. The hope is that ministerial approval might be delegated to health research ethics committees.

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Introduction: historical note and development of international guidelines

The default doctor-patient relationship in the clinical setting has traditionally been one of paternalism: the doctor makes decisions regarding the patient's health and treatment with limited or no input from the patient.[1, 2] This view has until recently informed the doctor-patient (and researcher-patient) relationship in the research setting. Several enlightened physicians and researchers voiced contrary views in the last decades of the 19th, and the first half of the 20th centuries, only to have their ideas thwarted by their peers; for example, in 1907, William Osler (unsuccessfully) promoted the idea of informed consent in an address to the Congress of American Physicians and Surgeons.[3] In a 1916 JAMA article, Cannon suggested that the American Medical Association (AMA) adopt a formal code of research ethics centralising informed consent, again rejected by the AMA.[3]

Contemporary codes and guidelines for ethical health research developed in response to the Nazi atrocities exposed at the post-war Nuremberg trials of Nazi doctors.[4] Landmark dates and publications are the Nuremberg Code (1947),[5] the World Medical Association (WMA) Declaration of Helsinki (1964, and numerous consequent revisions to 2008),[6] in the USA, the Belmont Report (1979),[7] and the

Council for International Organizations of Medical Scientists (CIOMS)/WHO international guidelines on human research.[8] Table I lists some of the more important international guidelines. Central to all of these are the principle of informed consent, and the primacy of the interests of and protection of research participants (subjects).

Ethical principles and informed consent in human health research

Emanuel et al[9] described a framework consisting of eight principles for ethical human research in developing countries, and developed a series of benchmarks to further illuminate these principles. Whereas the principle of collaborative partnership may not be applicable to most anaesthesia/ICU research, all their other principles are:[9]

- Social value: society, or a subsection of society (e.g. a vulnerable group of participants) should benefit from the research; the beneficiaries and potential benefit should be identified.
- Scientific validity: it goes without saying that all proposed research should be scientifically sound in relation to its social value. This implies that research design should ensure that the questions posed could potentially be answered, and that the study is practically feasible.
- Fair selection of study population: Selection should ensure scientific validity, the minimisation of risks and protection of vulnerable persons, particularly in anaesthesiological research.
- Favourable risk-benefit ratio: If participants are exposed to additional risks, these should be favourably balanced by potential benefit to themselves or other identifiable groups (e.g. society in general, the community of patients).
- Independent review: All forms of review mandated by laws and/or regulations should be undertaken by competent review committees; this ensures accountability and transparency. Research ethics committees' primary function if to protect participants from abuse, harms and risk.
- Respect for participants: Benchmarks are maintenance of confidentiality, ensuring that participants are free to withdraw at any time, providing participants with information arising from the study, and prevention and treatment of study-related harms.
- Informed consent: Information should be provided and consent obtained in culturally and linguistically appropriate format.

Without denying the importance of other principles (*all* principles should be respected), the intention of this article is to focus on the central principle: that of *informed consent*.

Informed Consent refers to the written (i.e. documented), dated and signed decision to take part in a research project or clinical trial "taken freely after being duly informed of its nature, significance, implications and risks" by a competent adult.[10] Recruitment of potential participants may not commence without prior written consent unless this requirement has been specifically waived by the health research ethics committee (HREC) consequent to a formal, written application by the researchers.

There are both philosophical-ethical and legal imperatives for the practice of informed consent.[3,4] From an *ethical* viewpoint, for example, Immanuel Kant admonishes us never to treat humans (including the self) only as means to an end, but always also as ends unto themselves.[11] In practice this means treating humans with due respect while promoting inherent human dignity and recognising them as persons. A primary expression of respect is recognising that persons are entitled to decide their own destiny, to make informed choices.

Valid informed consent is a *legal and legislative* prerequisite to ethical research.

Table I. Important international health research guidelines

- 1947 Nuremberg Code
- 1948 United Nations General Assembly (UNGA) Universal Declaration of Human Rights
- 1966 UNGA International Covenant on Civil and Political Rights.
- 1964 World Medical Association (WHO) Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (current version 2008; 2014 proposed revision posted for comment)
- 1979 Belmont Report
- 1982 Council of International Organisations of Medical Scientists (CIOMS) *International Ethical Guidelines for Biomedical Research Involving Human Subjects*
- 1991 CIOMS *International Guidelines for Ethical Review of Epidemiological Studies*
- 1993 CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects*.
- 1995 WHO *Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products*
- 1996 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) *Guideline on Good Clinical Practice*
- 2000 Joint UN Programme on HIV/AIDS UNAIDS Guidance Document *Ethical Considerations in HIV Preventive Vaccine Research*; updated 2007 as *Ethical Considerations in Biomedical HIV Prevention Trials*
- 2004 WHO A Practical Guide for Health Researchers
- 2008 CIOMS *International Ethical Guidelines for Epidemiological Studies*
- 2009 WHO Casebook on Ethical Issues in International Health Research
- 2010 Singapore Statement on Research Integrity
- 2012 Ottawa Statement on the Ethical Design and Conduct of Cluster Randomised Trials

Current South African health research regulation

The US Code of Federal Regulations defines research as follows: *Research* is a formal and systematic investigation, including research development, testing and evaluation, aimed at the development of or contribution to generalisable (new) knowledge (with the eventual purpose of changing practice).[12] (Bracketed sections author's addition/ clarification.)

Health research is defined quite expansively in Section 1: Definitions, of the National Health Act, Act 61 of 2003 (NHA)[13], including any research which contributes to knowledge of:

(a) the biological, clinical, psychological or social processes in human beings;

(b) improved methods for the provision of health services;

(c) human pathology;

(d) the causes of disease;

(e) the effects of the environment on the human body;

(f) the development or new application of pharmaceuticals, medicines and related substances and

(g) the development of new applications of health technology

The last two items define clinical trial research.

All health research falling under the above definitions is strictly regulated. A common thread running through all principles, guidelines, acts and regulations is that no health research may commence without *prior written approval by a duly constituted HREC* registered with the SA National Health Research Ethics Council (NHREC), a statutory body.

SA legislation/regulation comprises:

1. The Constitution of South Africa:[14] The SA Bill of Rights[15] has important inferences for ethical health research, particularly underwriting the importance of informed consent. The *right to equal treatment* implies fair selection of research participants. *Respect for the inherent dignity of all persons* implies that certain types of research which might impact on human dignity are unacceptable and supports the notion of informed consent. The *right to freedom and security of the person* implies that scientifically unsound research or absence of proper informed consent is a constitutional violation. The *right to privacy* requires private consultation with potential participants. The *right to bodily and psychological integrity*, including security in and control over one's body, and not to be subjected to medical or scientific experiments without one's legitimate prior informed consent, is unequivocally protected in paragraph 12.2.
2. The NHA[13]**:** Section 73 regulates the functioning and responsibilities of HRECs, inter alia to evaluate and approve research that meet their standards and norms, based on current SA legislation and regulation/guidelines, and national and international standards, norms, practices, guidelines and codes of conduct. Section 73 mandates *prior* approval of all health research by a HREC.
3. Department of Health Guidelines: The SA National Department of Health (DOH) has published two sets of *guidelines* for RECs. Both Ethics in Health Research: Principles, Structures and Processes, DOH, 2004 (DOH 2004)[16] and Guidelines for Good clinical Practice in the Conduct of Clinical Trials with Human Participants, 2nd Edition (SA GCP)[17] mandate prior informed consent before commencement of a study. Researchers undertaking clinical research are required to submit currently valid GCP certification to the appropriate HREC.

Other national guidelines include the Medical Research Council (MRC) Book 1: Guidelines on Ethics in Medical Research: General Principles;[18] and the Health Professions Council (HPC) Booklet 6: Guidelines for good Practice in Health Research.[19] These publications are readily accessible online. HPC guidelines apply to health professionals registered with the Council. All health related research done in SA must conform to these principles, guidelines, acts and regulations.

Anaesthesia research presents unique challenges

Anaesthetised patients are extremely vulnerable to researcher abuse due to the nature of anaesthesia, extreme dependency, vulnerability and loss of consciousness (i.e. the ability to question and fend for oneself), and the combined roles of researcher and clinician.[1] Whereas rigorous adherence to the principle of informed consent is normally sufficient to ensure protection of research participants, in anaesthesia more is required, and the integrity of the researcher becomes equally important. A further safeguard, though not guarantee, is that researchers doing clinical research (this includes all drug/medical device related research) are required to undergo formal Good Clinical Practice training, hold valid GCP certification, and need to know and adhere to the stipulations of SA GCP.[17]

The default informed consent requirement is that fully informed and accurately documented prior written consent is mandatory in all *prospective* research, including all sampling and data collection done for research purposes. When data is derived from, for example, clinically indicated samplings, graphs, and ultrasound tracings, participants should consent thereto, as they should to all blood/urine sampling for research purposes. Collecting data without valid informed consent not only violates the trust placed in researcher/clinicians, but also harms participants because their privacy is violated, irrespective of whether they are aware of this, and this impacts on their human dignity. Participants should clearly understand which aspects of procedures denote *treatment*, and which *research*, and consent thereto. Procedures which might in clinical scenarios form part of routine care must now, when they are performed as part of a research protocol, be fully explained to participants and consented to. Treatments, interventions and measurements which form part of research should thus be clearly distinguished from the same procedures that are exclusively part of clinical care. More generally, in research the aim is usually not to benefit the individual participant (the exception is therapeutic research) but to answer a research question (or hypothesis) using a strictly defined and adhered to methodology; in clinical care, the intention is invariably to promote the interests of the individual patient using evidence based treatment modalities usually contextually adapted. In clinical anaesthesia research the distinction may not be as apparent and clear as stated above, and it is advisable that the research protocol clearly lists therapeutic versus experimental procedures and measurements/interventions.

The latter should also be apparent in the patient information and consent document. Note that HRECs may have limited appreciation of the complexities of clinical anaesthesia and anaesthesia research.

Children require additional protection. The age of consent for research remains 18 years, the age of majority as per the Children's Act (Act 38 0f 2005).[20] HRECs apply stringent criteria in non-therapeutic research on minors, and generally only approve low-risk studies, or moderately risky studies aimed at answering questions directly related to the vulnerable group which could not be obtained from adult research, or high-risk studies when they are therapeutic. HRECs do accept that in order to advance the quality of care, research on children may be required, just as it may be required on ICU patients, pregnant women and other vulnerable groups. The key principle is that the vulnerable group must be advantaged by the research. Research should not be performed without co-consent (children 14 and older), and assent (children 7 and older) and minors should be co-opted into the consent process considering their level of understanding and insight.

Waiver of individual informed consent is usual for retrospective data analyses with minimal risk to participants. Minimal risk implies that not exceeding the hazards experienced in normal life or normal non-invasive treatment. In this case, the only discernible hazard would be violation of confidentiality and privacy. To warrant waiver of consent, the researcher must confirm that data will be collected totally anonymously with no identifying links, or that such links will be access-protected to protect confidentiality.

Case reports not identifying patients should be presented to the HREC in completed form together with a simplified consent of the patient wherever possible.

Quality-improvement audits may be done without HREC approval, but whenever possible and feasible with patient consent. Such data may be used internally (within a group, a practice, a department or even an institution). Note however that retrospective HREC evaluation and approval is not possible, and whenever the possibility of wider distribution (generalisation) of results may be envisaged, for example publication or congress presentation, prior ethics approval is advised. In teaching hospitals, HREC approval is advised to cover this eventuality.

Vulnerability of ICU patients and informed consent in ICU research

All patients and research participants are vulnerable; ICU patients are uniquely vulnerable. They are acutely and usually desperately ill, mortality and morbidity rates are known to be high, and participants/relatives may be susceptible to coercion. Financial considerations (e.g. free study medication to replace expensive standard care drugs) may unduly influence decisions. Patients are captive and highly dependent upon their caregivers/doctors who have a dual role, increasing the risk of harm due to conflicts of interest. They are particularly susceptible to therapeutic misconceptions which may occur in RCTs (randomised controlled trials), erroneously believing that research "treatments" are in their interests, and/or personally tapered, clear information to the contrary notwithstanding [21, 22] They are often in higher age brackets, increasing attendant risks and difficulties. They commonly have diminished cognition of varying degree due to underlying disease, the psychological effects of ICU treatment, sleep deprivation, light to deep sedation (e.g. when ventilated), and therefore may have diminished comprehension of the nature of envisaged research, and may lack the capacity to provide authentic informed consent.[22] The vulnerability of critically ill patients is exacerbated when they become research subjects. In South Africa language and education barriers are often confounders, as is (rural) patients' scientific and technological naiveté. Diverse cultural and religious beliefs are additional obstacles which medical personnel with scientific views of medicine may not fully contextualise.

Relatives and other representatives find the unexpected responsibility of making treatment related surrogate decisions problematic. Providing authentic surrogate consent for research which is difficult to comprehend, may not benefit and may add to risk may entail an unreasonable additional burden.[22] Surrogates simply may not know what their wards might have chosen: in several studies correspondence between family members' predicted opinions and subject preference in fictitious ICU scenarios varied from 51-88%.[22]

The ICU environment is not conducive to the quiet contemplation required for participants to authentically evaluate options and make decisions about consenting to research.

The current (2008) version of the Helsinki Declaration mandates that comparators in comparative studies should be "best current proven" interventions unless no such consensus exists, or sound methodological reasons for non-standard of care comparator can be argued.[6] Disagreement on standard of care in the ICU may introduce additional uncertainty regarding the notion of clinical equipoise, genuine evidence based uncertainty about particular treatments, without which clinical research is unjustified. Protocolised care, the basis of all RCTs, may be especially problematic to explain, since ICU care is usually extremely individualised. Conflicts of interest which could affect patient care should be disclosed.

As in anaesthesia research, the primacy of patient interests, informed consent (problematic as it may be),[22] re-consenting if/when patients sufficiently recover, strict adherence to approved research protocols, the guidelines contained in SA GCP[17] and to any protective requirements additionally requested by the HREC, and continued HREC oversight, coupled with researcher integrity and responsibility serve to protect participants from harm.

Finally, clinical trials have set goals or end points. The aim of regular evidence-based treatment is patient benefit; non-therapeutic trials are designed to test hypotheses or deliver benefit which may advantage others but not the patient. There is thus tension between the ethical demands of beneficence and trial demands, and the rights of the individual versus common benefit.

Consent in emergency and ICU care: SA regulatory guidelines

When individual informed consent as prescribed is not possible (coma, emergency, temporary mental incapacity, certain forms of mental health research) DOH 2004 determines that prior HREC approval must be obtained "in all situations in which it is justifiable to initiate research without the informed consent of the participant".[16] Research requiring special attention include participants in dependent relations and those undergoing emergency care. DOH 2004 recognises the need for research in emergency care in order to improve care, and that informed consent is not always possible. The justification of research without individual consent is restricted to scientifically valid research which *offers realistic possibilities of benefit over standard care* and which is not contrary to patient's interest, or therapeutic research without increased risk.[16] The patient, upon recovery, or next of kin or legal guardian should be informed as soon as feasible, and consent confirmed. Because of extreme vulnerability such persons "*should be excluded from all but minimally invasive observational studies*". Unless advance consent was obtained upon admission (which is seldom possible or practicable), these requirements must be met before a HREC can approve a study without prior participant consent. SA GCP notes the fundamental difficulties of consenting non-conscious persons.[17] Some form of proxy/surrogate consent, or consent by a statutory body on behalf of extremely vulnerable persons is the only possibility, thus again "*unconscious patients should be excluded from all but minimally invasive observational research*". When the principle of informed consent cannot be honoured, and advance consent has not been given, a HREC may approve a research project without prior consent with provisos as set out above. Care should be taken that the dependency of the patient as such is not coercive influence. However, if applied to the letter, these regulations would severely limit legitimate ICU research. HRECs are independent, autonomous, capable and responsible bodies with sufficient authority (mandated by Section 73 of the NHA)[13] to nuance and contextualise the apparent constitutional/regulatory limitation of informed consent/ICU research. They may waive individual informed consent in minimal risk studies, or may approve surrogate decision making in exceptional cases, to facilitate important intensive care (ICU) research which otherwise could not have been done (a practical example of the latter is a study relating to treatment in severe sepsis where immediate enrolment may be required and participants are incapacitated; a close relative would be the preferable surrogate, but if unavailable, an informed ICU physician not involved in the research may be a valid alternative).

The dilemma of NHA Section 71

Section 71 of the NHA[13] which has only recently been promulgated states that irrespective of any other law, individual written informed consent is a *necessary pre-requisite* for legitimate human research or experimentation. Section 71 has two important implications:

- It mandates individual participant informed consent in all instances and forms of health research (as defined in the NHA);
- It effectively limits research on minors (under 18s) to therapeutic research (i.e. research which is expected to benefit the participant), unless approved by the Minister.

Although apparently in line with the Bill of Rights (12.2, see above) and other guidelines, Section 71, if applied, would ***mandate*** impracticable, contra productive and/or unreasonable demands from researchers. Low-risk, anonymous, confidential, retrospective record reviews for which individual consent is now usually waived, would, for example, necessitate individual informed consent, and many currently ongoing studies might have to be discontinued. Section 71 is inconsistent with current international and local practices, is internally inconsistent with other Sections of Act 61 (e.g. it limits the authority of HRECs as mandated by Section 73), and externally inconsistent with other Acts. Section 71 would particularly problematise research on minors; such research could only take place if it is *therapeutic* (with, as before, the consent of the parent or legal guardian). All *non-therapeutic* research involving minors would require the approval of the Minister of Health which may not be given if the objects of the research can be achieved from research on adults, if the results are unlikely to benefit the minor or other minors, if the consent process is contrary to public policy, and if there is considerable risk or unfavourable risk-benefit ratio. Section 71 would thus seriously limit research on children, questioning the legitimacy of almost all such current research, and make the approval process unmanageable. At a joint 2012 meeting of SA HREC chairpersons, a decision was taken (supported by the HREC registering body, the NHREC) to defer application of Section 71 pending further interaction with the Minister of Health.[23] The latter decision has been ratified by most academic institutions where health research is performed. Regulations pertaining to Section 71 were recently published for comment;[24] many of the problematic issues remain, but there is now provision of the delegation of ministerial approval, and hopefully this would include delegation to registered HRECs. HRECs do have the authority to interpret and juxtapose conflicting legislation in order to fulfil their role. This position was affirmed at a June, 2013 meeting of HREC chairs.[25]

Concluding comments

Unique challenges face the anaesthesiologist and intensivist conducting clinical research. These are often

not readily recognised by researchers who may find it difficult to understand why routine clinical procedures and measurements, when performed in a research setting, suddenly fall into a different category, placing greater demands on the authenticity of informed consent, for example. Consent in temporarily incompetent adults is particularly problematic and if strictly applied, SA legislation/regulation forbid all but therapeutic (aimed at treatment) or minimally invasive, observational research on these patients. However, HRECs appreciate that for obvious reasons, anaesthesia and ICU research are critically important and necessary, and will, for example, permit surrogate decision making where appropriate. Implementation of Section 71 of the NHA as originally intended would compromise research on temporarily incompetent adult ICU patients and children.

The original codes/declarations for ethical human research (e.g. Nuremberg, Helsinki), which form the basis of current guidelines/regulations, predate the development of critical care as a common form of treatment and consequent research. These guidelines/regulations have not adequately been updated to cater for new and novel challenges, are in urgent need of revision and should be updated to unequivocally provide guidance and accommodate the realities of current ICU care and research in the light of international trends and practices.

In particular, alternatives to standard forms of consent (deferred consent, prospective consent, waivers of consent and particularly surrogate consent) should be addressed in the light of international experience.[26,27,28] Since our prime concern is the prevention of harm to participants, an added safeguard that could be mandated is an informed, but independent patient advocate who might be better equipped to provide surrogate consent in temporarily incompetent ICU patients; this would be an informed clinician involved neither in the trial nor the treatment of the individual.

All institutions that conduct health research (for example medical schools) are legislatively obliged to have on-site research ethics committees. It may be advisable to consult with the local committee (and the resident statistician) in the *planning* phase of proposed research; this may prevent unnecessary delays in approval. HRECs usually have informative and helpful websites and researchers should become familiar with the standard operating procedures of respective committees.

References

1. De Roubaix JAM. Guest editorial: Seeking patients' consent in anaesthesiology: consent in clinical practice. SAJAA 2005;11(4)125-129
2. De Roubaix JAM. Informed consent for anaesthesia in ambulatory surgery: A South African Perspective. Ambulatory Surgery 2006;12(4)199-205. Review article.
3. Blacksher E, Moreno JD. A history of informed consent in clinical research. In: The Oxford Textbook of Clinical Research Ethics, eds. Emmanuel EJ, Grady C, Crouch RA, Lie RK, Miller FG and Wendler D, Oxford University Press, Oxford & New York, 2008, pp591-605.
4. Weindling PJ. The Nazi medical experiments. In: The Oxford Textbook of Clinical Research Ethics, eds. Emmanuel EJ, Grady C, Crouch RA, Lie RK, Miller FG and Wendler D, Oxford University Press, Oxford & New York, 2008, pp18-30.
5. Nuremberg Code. http://ori.dhhs.gov/education/products/RCRintro/c03/b1c3.html Accessed 29 May 2013
6. World Medical Association Declaration of Helsinki, 2008. www.wma.net/en/30publications/10policies/HB-E-2011.pdf Accessed 29 May 2013.08.06
7. Belmont Report. www.fda.gov/2005-4178b_09_02 Belmont_Report.pdf http://www.fda.gov/oc/ohrt/irbs/belmont.html Accessed 29 May 2013
8. CIOMS *International Ethical Guidelines for Biomedical Research Involving Human* 8. *Subjects*, 1993. www.cioms.ch/publications/layout_guide2002.pdf Accessed 29 May 2013
9. Emanuel EJ, Wendler, D, Killen J and Grady C. What makes clinical research in developing countries ethical? The benchmarks of ethical res earch. JID 2004;(189)5:930-37 http://www.jstor.org/stable/30075913 Accessed:23April 2013
10. Guidance for applicants: Informed consent. European Commission - Research Directorate-General; Directorate L - Science, Economy and Society; Unit L3 - Governance and Ethics ftp://ftp.cordis.europa.eu/pub/fp7/docs/informed-consent_en.pdf (adapted) Accessed 29 May 2013
11. Kant I. Grounding for the metaphysics of morals. 1785; translated by Ellington JW, 1993, p30
12. 45 CFR 46: U.S. Department of Health and Human Services www.hhs.gov › ASH › OHRP Home › Regulations Accessed 29 May 2013.
13. National Health Act, Act 61 of 2003. 23 Jul 2004 – Government Gazette, Republic of South Africa. Vol. 469, Cape Town 23 July 2004. No 26595.
14. South African Constitution Act, Act No 108 of 1996 www.info.gov.za/documents/constitution/1996/a108-96.pdf Accessed 29 May 2013
15. South African Constitution Act, Act No 108 of 1996, Chapter 2. http://www.info.gov.za/documents/constitution/1996/96cons2.htm#10 Accessed 29 May 2013
16. Ethics in Health Research: Principles, Structures and Processes, Department of Health, 2004 www.doh.gov.za/docs/policy/.../researchethics.pdf Accessed 29 May 2013
17. Guidelines for Good clinical Practice in the Conduct of Clinical Trials with Human Participants, 2nd Edition, Department of Health, 2006. www.kznhealth.gov.za/research/guideline2.pd Accessed 29 May 2013
18. Medical Research Council (MRC) Book 1: Guidelines on Ethics in Medical Research: General Principles. www.mrc.ac.za/ethics/ethics.htm Accessed 29 May 2013
19. HPC guidelines Health Professions Council (HPC) Booklet 6: Guidelines for good Practice in Health Research. https://www.google.co.za/search?q=hpcsa+booklet+1&ie=utf-8&oe=utf-8&aq=t&rls=org.mozilla:en-US:official&client=firefox-a Accessed 29 May 2013
20. Children's Act, Act 38 of 2005. www.justice.gov.za/legislation/acts/2005-038%20childrensact.pdf Accessed 29 May 2013
21. Appelbaum PS, Roth LH & Lidz C. The therapeutic misconception: informed consent in psychiatric research. Int J Law & Psychiatry 1982; 5:319-329 http://cirge.stanford.edu/Apr%2018%20-%20Therapeutic%20misconception/Appelbaum%20Therapeutic%20Misconception.pdf Accessed 29 May 2013
22. Luce JM. Is the concept of informed consent applicable to clinical research in critically ill patients? Crit Care Med 2003(31)S153-S160
23. Unpublished: Meeting of HREC chairs held in Pretoria, June 2012.
24. SA Government Gazette No9966, Vol575 No36508, 29 May, 2013. Government Notice R.378: Department of Health: National Health Act (61/2003). Regulations relating to research on human subjects
25. Unpublished: Meeting of HREC chairs held in Pretoria, June, 2013
26. Gray JD. The problem of consent in emergency medicine research. CJEM 2001,3(3);213-218. Online http://www.cjem-online.ca/v3/n3/p213 accessed 31 July 2013
27. The problem of informed consent in emergency medicine research. Emerg Med J 2001,18:198-204. Online http://m.emj.bmj.com/content/18/3/198.full Accessed 31 July 2013.
28. Halila R.Assessing the ethics of medical research in emergency settings: how do international regulations work in practice? Sci Eng Ethics 2007,13(3):305-313. Online http://www.ncbi.nlm.nih.gov/m/pubmed/18210225/. Accessed 31 July 2013.