



Research protocols — lessons from ethical review

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To the Editor: The aim of this study was to document the decisions made by the University of Cape Town (UCT) Research Ethics Committee (REC) and to identify the reasons for rejection or acceptance of protocols subject to additional requirements/conditions. Identifying ethical problems that are grounds for rejection of protocols can assist in educating researchers on these issues and facilitate the implementation of well-designed, socially valuable research.

The establishment and support of human RECs is considered a major priority by the Secretary General of the Council for International Organizations of Medical Sciences (CIOMS).¹ The terms of reference of RECs require the boards 'to review and recommend modification, if needed, of research protocols, to reject irresponsible protocols and to monitor ongoing projects'.²

The UCT REC currently reviews 300 - 400 research protocols per year originating from UCT or affiliated hospitals. UCT has not previously documented the number and nature of protocol acceptances and provisional and absolute rejections by its REC. Similar studies have been conducted elsewhere but there are few research overviews of REC stipulations in the literature.³ Audits of practice can provide useful information to institutions and researchers³ and result in a reduction in approval time.⁴ They can also assist academic institutions in monitoring their faculty research priorities.

Methods

We used a retrospective, descriptive study design and analysed all protocols considered by the REC of UCT from January to June 2002. Descriptive statistics were used to describe the numbers, types of studies, etc.

Data sources included the official application form for ethical approval, the submitted protocol, the written comments of the reviewers and the correspondence of the chairperson of the REC and the principal investigators (PIs).

Approval was obtained from the REC to undertake the study and access the protocols, respecting the confidentiality of any proprietary information.

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Results

A total of 197 protocols were reviewed, of which 189 were included in the analysis; 24% were for contract research (i.e. research sponsored by commercial sources, such as pharmaceutical companies), 44.4% for postgraduate degree purposes and 31% were investigator driven. Ninety-eight protocols (50%) required resubmission with amendments and 173 protocols (91.5%) were ultimately approved. The mean time from submission to final approval of the protocols was 2.0 months (standard deviation (SD) 1.5 months, range 1 - 10 months). There were 254 stipulations, most related to a favourable risk-benefit ratio (23%) and aspects of informed consent (24%), followed by problems with scientific validity (17%), fair subject selection (13%), independent review (procedural amendments required) (11%) and respect for persons (10%). There were few stipulations regarding social or scientific merit (2%).

HIV/AIDS was the most common condition researched (13%), followed by sport-related injuries and related exercise physiology (11%) and conditions affecting the respiratory tract, including research on asthma and rhinitis (9.5%).

Outcome of submission

Ninety-eight protocols (50%) required resubmission with amendments. The mean time from submission of the protocol to communication of the amendments required by the REC was 1.24 months (SD 0.59 months, range 0.27 - 3.4 months). Ultimately 173 protocols (91.5%) were approved. The mean time from submission to final approval of the protocols was 2.0 months (SD 1.5 months, range 1 - 10 months). Excessive delay in approval was due to the PIs having to consult with sponsors, waiting for South African Medicines Control Council approval or not submitting all the documentation required. REC administrative problems, including delayed reviewer response, caused delays in three cases.

Ethical objections

Frequently more than one ethical objection was raised per protocol.

Incorrect submission procedure resulted in return of 11% of the protocols. This included incomplete application forms, submission without proof of approval from the Medicines Control Council and inadequate disclosure of financial or other conflicts of interest.



Scientific validity amendments were requested in 22% of the studies. The Nuremberg Code⁵ and the Declaration of Helsinki⁶ state that good scientific methodology is a prerequisite for ethical justifiability.⁷ Problems included inadequate definition of terms, inappropriate research design, poor description of inclusion criteria, inappropriate use of English measurement outcomes in subjects from other language groups and inadequate description of statistical methods.

The informed consent process was often (20%) the subject of REC stipulation as in other studies.³ Information sheets were found to be too technical, badly phrased, poorly translated or misleading. Inadequate information was the most common objection (13%). Information regarding the risks, benefits, alternative treatments available, time commitment, and potential payment, was frequently missing. Information related to HIV testing was sometimes found to be inadequate. Several protocols did not mention the need to obtain assent from minors and there was often confusion regarding the age of consent (legally 21 years of age).

Beneficence or the well-being of the subjects, specifically safety and subject protection issues, gave rise to 22% of the objections. A recurring issue was the insurance cover of participants. In non-contract research there was concern that the participant was not covered for any research-related misadventure on a no-fault basis, apart from the researchers' professional malpractice insurance. There was considerable debate on how to proceed with protocols that included monitoring different aspects of the health and functioning of people living with HIV but without access to antiretroviral therapy. PIs were ultimately requested to insert a clause that they would ensure that the participants in their study would be given access to antiretroviral therapy if it were to become available and that any study researching the 'natural course' of the disease would cease.

Justice or equity-related concerns were raised in 12% of stipulations. The REC insisted that the 2000 version of the Helsinki declaration be cited (7% of objections). Article 30 states: 'At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study',⁶ particularly with regard to the provision of post-trial drugs where applicable and feasible. Queries were frequently raised regarding the choice of disadvantaged subjects or the exclusive use of developing countries, including South Africa, as subjects/sites for research.

Confidentiality or autonomy issues were raised in 13% of cases. Several protocols were rejected as they proposed recruitment of participants from existing patient records, without first obtaining permission from the participants. Others failed to state how samples and data were to be stored to ensure confidentiality of the information.

Discussion

A wide range of protocols was reviewed, varying in purpose, design and health conditions studied. Based on these results, investigators should adhere closely to the submission formalities with regard to financial disclosure. Protocols should reflect scientific rigour, a clear description of the methodology and data analysis. It should be clearly indicated that the welfare of subjects is a primary concern and that adequate, readily accessible insurance cover is provided to the participants.

Informed consent documentation should be comprehensive and written in language at an appropriate level, with minimal recourse to technical terms. Guidelines are available regarding essential information that should be included in informed consent documents, including that of the Medical Research Council of South Africa,⁸ which researchers should consult to prevent requests for amendments.

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