Chapter 16
Ethics of Clinical Research

16.1 Introduction

Ethics, an essential dimension of human research, is considered both a discipline and practice. For clinical research, ethically justified criteria for the design, conduct and review of a clinical investigation can be identified by obligations to both the researcher and human subjects. Informed consent, confidentiality, privacy, privileged communication and respect and responsibility are key elements of ethics in research [1].

The ethical conduct of a clinical trial does not end with the formulation of the study design and a signature on an ICF. Protecting the rights, interests and safety of research subjects must continue throughout the study duration. Subject safety monitoring is the responsibility of several groups, including RECs or IRBs, investigators and their research staffs, sponsors and DMCs, also called DSMBs, especially in the USA. Reports during the last few years of the deaths of research subjects and deficiencies in the monitoring of clinical trials have raised serious concerns regarding the systems and processes by which subject safety is currently monitored [2–5].

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16.2 Research Ethics' Declarations

There are treaties and declarations for the fundamental principles of ethical conduct in biomedical research: the Nuremberg Code [6], the Declaration of Helsinki [7], the EU Convention on Human Rights and Biomedicine [8], the Convention on Human Rights and Biomedicine (the Oviedo Convention) [9], various guidelines promulgated by the Council for International Organizations of Medical Sciences [10] and a number of treaties and conventions [11–14]. Principles have been enunciated specifically to protect human subjects from harm and to demonstrate respect for their autonomy. The two comprehensive and pioneering documents about research ethical issues are considered to be the Nuremberg Code and the Declaration of Helsinki.

16.2.1 Nuremberg Code (1947)

In the twentieth century, the judgement of the trial of Nazi doctors at Nuremberg is the commonly recognised starting event for modern research ethics. It contained ten paragraphs, referred to as the Nuremberg Code [6]:

No. 1: Voluntary consent is to be based on sufficient knowledge of the nature, duration, purpose, methods, inconveniences, hazards, and effects of the research.
No. 2: Research is expected to yield fruitful results for the good of society not procurable by other methods.
No. 3: Research is to be based on animal research and prior knowledge.
No. 4: All unnecessary physical or mental suffering and injury are to be avoided.
No. 5: No experiment is to be conducted in which death or disabling injury will occur (except where physicians are also subjects).

No. 6: Degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved.
No. 7: Preparation and facilities are provided to protect subjects against even the remote possibility of injury, disability, or death.
No. 8: The research is to be conducted by scientifically qualified persons and requires the highest degree of skills and care.
No. 9: Subjects are free to bring an experiment to an end if they have reached the physical or mental state where continuance seems impossible.
No. 10: Researchers are to be prepared to terminate the experiment if they have cause to believe, according to their good faith, skill, and judgment, that continuation is likely to result in injury, disability, or death to a subject.

16.2.2 Declaration of Helsinki

In 1964, the Declaration of Helsinki, published by the World Medical Association, introduced an authoritative attestation of the need for prior review of any kind of human research [7]. Although the Declaration emphasised the scientific standards that should govern scholarly research, it allowed more freedom to physicians to omit the application of consent procedures in special circumstances [15]. This shortcoming of the Declaration indicated that the rights and safety of research participants still lay with the individual investigator. Today, the Declaration of Helsinki is considered a document of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

16.3 Research Ethics Committees (RECs) or Institutional Review Boards (IRBs)

RECs or IRBs [5, 16] aim to safeguard the welfare, dignity and safety of participants, ensure that ethically approved research is conducted in line with the approved protocol and promote public confidence in the conduct of human research. RECs play key roles in promoting ethical practices in biomedical research and in identifying solutions to ensure that the interests of researchers and society do not take precedence over the rights of the participants [16].

The IRB has numerous protection responsibilities that include initial and continuing review of the study protocol and related documents, review of the documentation of informed consent (though it is particularly difficult for IRBs to adequately monitor the informed consent process, even with unannounced 'spot checks') and review of reports of unanticipated problems and of AEs [5].

16.4 Data Safety Monitoring Boards (DSMBs)

The establishment of DSMBs was based on the recognition in the 1960s that independent means of interim monitoring of accumulating data were essential to determine ongoing subject safety in a trial. Essentially, individuals closely involved in trial design and conduct might not be fully objective in reviewing interim data for emerging concerns of harm to trial subjects. To provide the necessary monitoring, DSMBs usually consist of individuals with pertinent expertise in the disease under study, as well as statisticians, ethicists and sometimes community representatives [5].

DSMBs have been used increasingly due to the increasing number of industry-sponsored trials with mortality or major

morbidity endpoints, heightened awareness in the scientific community of problems in analysis that might lead to bias or inaccurate results and the previously mentioned concerns that IRBs are unable to properly monitor subject safety in multicenter trials [5].

The focus of DSMBs is on the total safety experience in a trial. The members of the DSMB therefore review aggregate data at predefined intervals and consider differences in the rates of clinical endpoints to determine whether clear benefits or harm might be occurring. They also review individual reports of AEs and consider the frequency, severity and types of AEs and serious adverse events (SAEs). A decision to stop a trial is made when, using preplanned statistical analyses, significant differences in either benefits or harm are observed among the study arms or when there have been an excessive number of AEs in one of the study groups [5].

16.5 Good Clinical Practice

'The cornerstone of sponsor and investigator responsibilities is the concept of good clinical practice, which is detailed in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline #6 [17]. GCP standards were developed to provide guidance to investigators that would result in common approaches to clinical trials performed in multiple countries. GCP forms a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials, thereby providing assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected. GCP has several objectives concerning the protection of trial subjects, quality of data, and transparency of trial conduct [17]'.

16.6 Important Topics for Research Ethics

16.6.1 Informed Consent

Informed consent refers to an ethical and legal doctrine based on the understanding that all interventions (diagnostic, therapeutic, preventive or related to scientific studies) in the medical field should be performed only after a participant has been informed about the purpose, nature, consequences and risks of the intervention and has freely consented to it [18]. The primary focus of consent should be on informing and protecting research subjects, through disclosure and discussion of relevant information, as well as by meaningful efforts to promote participants' understanding, and by ensuring that decisions to participate, or to continue participating, are always made voluntarily. Informed consent is the ethical cornerstone of RCTs, where volunteers are given the option to participate in a trial that includes randomisation or to remain outside the trial and receive traditional medical treatment. Mandatory conditions for an informed consent include provision of detailed information to a subject, adequate understanding of the information provided and expression of consent to, and/or authorisation for, the intervention [19].

The researcher's primary moral responsibility is to design a clinical trial that will answer a research question without exposing human subjects to undue risks in the process [20]. When fully informed subjects give their consent, they acknowledge their role as research participants and take responsibility for their designated roles. Assuming that the research question is significant, the trial is well structured and the risks to the individual patient are justified, the tension between collective ethics and individual ethics is obviated when individual subjects give their informed consent. This holds true if the primary intent of the investigator is to compare two treatments, not to provide better overall care to the subject [21].

16.6.2 Patient Information Sheet

Once informed consent has been obtained, the research subject is given a patient information sheet, detailing the following aspects of the study: (1) title of the research project, (2) invitation to participate in the research, (3) purpose and significance of research, (4) time commitments, (5) termination of participation and indication of voluntary contribution, (6) risks involved, (7) costs and compensation and (8) anonymity and confidentiality [1].

16.6.3 Confidentiality

Confidentiality means the non-disclosure of certain information except to another authorised person. The concept of confidentiality applies insofar as the information a person reveals to a professional is private and has limits on how and when it can be disclosed to a third party [22]. Various dimensions of confidentiality described in the literature include human rights, confidentiality in relation to young persons, domestic violence, true anonymisation of data, validity of consent for disclosure, cancer and genetic registers, fertility, involuntary disclosure and safeguards [23]. There is no breach of confidentiality if the following recordings, for any purpose, are used, as long as they are effectively anonymised [24]:

(a) Conventional X-rays
(b) Images taken from pathology slides
(c) Laparoscopic images of the inside of the abdominal cavity
(d) Images of internal organs and ultrasound images

16.6.4 Privacy

Privacy is the quality of being secluded from the presence or view of others. Privacy in research refers to the right of an individual to

make decisions concerning how much information about their physical status, health, social network and thoughts and feelings will be shared with investigators [25]. To protect the privacy rights of family members, researchers must be careful in determining whether family members should be considered as research participants.

16.6.5 Privileged Communication

Privileged communication includes conversations within the context of a protected relationship, such as that between the doctor and patient, therapist and client, attorney and client, husband and wife or priest and penitent; under the common law, such privilege involves a number of rules excluding evidence that would be adverse to a fundamental principle or relationship if it were disclosed [26]. Such communications are secure, are reliable and meant to be kept among the directly involved parties.

16.6.6 Respect and Responsibility

Respect in research refers to respect for people and respect for truth. People have the right to dignity and privacy (informed consent and confidentiality). Respect for truth implies probity and respect for the intellectual rights of others. All possible efforts should be directed to avoid plagiarism and making false conclusions by over- or underemphasising the results [27]. Responsibility for a human subject involves voluntary informed consent, avoiding deception, rewards and incentives, privacy and disclosure. Additionally, researchers are responsible for maintaining the reputation of educational research by adhering to the highest standards of quality research. When publishing the research, investigators should disclose any competing or financial interests [1].

16.7 Ethics for the Paediatric Population

The word 'child' is not limited to the age range of 2 to 11 years, as defined in ICH E11. Further subsets of the paediatric population, as defined in ICH E 11, are preterm newborn infants, term newborn infants (birth to 27 days), infants from 1 to 23 months and adolescents from the age of 12 up to, but not including, 18 years. By emancipation or when the child reaches adulthood during the time in which he or she is participating in the trial, an adolescent may become legally competent to make decisions and to give informed consent [28, 29]. It should be noted that these age groups correlate poorly with maturation, especially from the developmental point of view, and trials may be performed across age groups, with consequences for the ethical aspects of their conduct [28].

16.7.1 Informed Consent from a Legal Representative

As a child (minor) is unable to provide legally binding consent, informed consent must be sought from the parents/legal representative on the child's behalf. Article 4(a) of the Clinical Trials Directive requires that the specific and written informed consent of a parent/legal representative must be sought prior to enrolling a child in a trial. Information should be given by an experienced investigator, or his adequately trained delegate, to each parent, or the legal representative, regarding the purpose of the trial and its nature, the potential benefits and risks and the names of the investigators responsible for conducting the trial, with background professional information (such as education, work experience) and direct contact details (telephone and e-mail) for further information regarding the trial. The parent/legal representative should be given sufficient time and necessary information to consider the

benefits and risks of involving the child in the clinical trial. When providing such information, it is important to take into consideration the fear and uncertainty of parents, especially when they are inexperienced with respect to the child's condition. However, the parents/legal representative might need more in the way of detailed and explicit information and, hence, more time to reflect on the implications of consenting, especially since they bear the full responsibility for the child, unlike adult trials where the subject takes the responsibility for himself/herself [28].

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