Key issues of research with human participation

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Summary

Research seeks to contribute to generalizable knowledge about the human condition; Research has certain risks - physical, social, psychological, financial, juridical. Protection of safety, rights and welfare of human participants is paramount. Protection of human participants and data quality are main standards of Good Clinical Practices.Some aspects covered in this standard are not applicable to all types of research. The basic ethical principles in research are autonomy, justice, and beneficence/non maleficence. Core elements of informed consent are: disclosure, comprehension, decision making, voluntariness, free from coercion, provision of information. It should be in a language understandable by the participant, clear, unambiguous and non-technical, delivered in the most effective mannerbyinvestigators/designees.
Quality system is a formal system to strengthen organization by raising standards of work and ensuring all activities are done consistently in order to ensure that processes are reliable; data generated is credible, repeatable/reproducible, auditable, and transferable across international boundaries.
Abbreviation: *GCP-Good Clinical Practices*
Key words: *research ethics, Good Clinical Practices, project quality assessment, informed consent form, quality system.*

Introduction

Advancement of medical knowledge requires research expanded on human beings. Generally, scientific investigation has extended and enhanced the quality of life; for many citizens, scientific discoveries have improved conditions caused by disease or disability. The prospect of gaining such valuable scientific knowledge should not be pursued at the expense of human rights or human dignity [4,11].
It is important to realize different aspects in any research proposal related to human participants:

- ◊ Physical or psychological intervention or observation or other interactions;
- ◊ Collection, storage and dissemination of information or biological materials from individuals;
- ◊ Observing participants personal psychological state individually as well as within groups;
- ◊ Research, management of environmental factors that could incidentally expose individuals involved in study [9,10].

Good Clinical Practices (GCP) is an international ethical and scientific quality standard that ensures human participant protection and data credibility; rigid and onerous bureaucracy discourages use of GCP by researchers, when it is not legally required. It is to be particularly highlighted that GCP is currently required by regulation in the conduct of clinical trials[13].

However, it is to be emphasized that the underlying principles of ethics and quality are applicable in any type of research involving human participants. Good Health Research Practices (GHRP) has been developed to adapt the principles of GCP to the context of research involving human participants beyond clinical trials[13].

Research ethics ensures the protection of rights, safety and well being of research participants and quality to ensure generation of credible research data[8].

Definition

Declaration of Helsinki is the leading international ethical standard for all research involving humans, their data or their tissue, was first adopted version in 1964 and since undergone several revisions[11].

CIOMS (Council for International Organizations of Medical Sciences) facilitates and promotes international activities in the field of biomedical sciences[12].

Ethics is moral principles that govern a person's behaviour or the conducting of an activity. It covers our rights and responsibilities and includes our behaviour in relationship with others.

Research basic ethical principles arejustice, beneficence/ non-maleficence, autonomy. Autonomy covers respect for persons, the right for an individual to make his or her own choice, protection of persons with impaired or diminished autonomy, i.e. vulnerable groups, informed consent, and privacy and confidentiality[3,4,5]. Autonomy indicates respect for persons' choice to decide for themselves whether participate in the research or not.

Justice includes some important aspects, such are: to treat each person according to what is morally right and proper, equal distribution of both burdens and benefits of the

research, research is responsive to the health needs of study population and has to ensure reasonable availability of research product /service development [3,5].

Beneficence/non-maleficence covers the ethical obligation to maximise benefits and minimise harms. The term *risk* refers both to the probability of a harm resulting from an activity and to its magnitude. Risk often stands for the combined probabilities and magnitude of several potential harms. *Benefit* refers to any favorable outcome of the research to the individual or to society. Benefit often stands for the combined probabilities and magnitudes of several possible favorable outcomes.

Types of risks are: physical (bodily harm, simple inconvenience), psychological (emotional suffering, breach of confidentiality), social/cultural (social discrimination, stigmatization), economic risks (financial costs related to participation), legal (abuse/violence/criminal prosecution).

Types of benefits are: physical (improvement of physical condition), psychological (feeling of well being; relief from suffering, willingness of supporting others in the future), economic (earning honorarium).

Informed consent is decision to participate in research made by acompetent individual who has received thenecessary information; has adequately understoodthe information; and after considering theinformation, has made decision withouthaving been subjected to coercion, undue influence, inducement or intimidation.

Informed consent form involves statement about purpose of research, description of procedures including all invasive procedures; randomization if any considered, foreseeable risk (pain, discomfort), expected benefits (if any), payment (amount, frequency and time). Also it covers information for participant in case of adverse events or injuries related to research (compensation, if available), volunteering, right to refusal/withdrawal from the research, confidentiality and its limits (who will have access to their data), expected duration of participation, foreseeable circumstances in which participation may be terminated, contact details for obtaining further information on research. In case of child's participation in research, parent/guardian signature is sufficient according to the law. Assent is not legally binding, however, is favoured by many Ethical Committees. There may beused age-appropriate information sheets for children (e.g.<5yrs, 6-12yrs, 13-15yrs and >16yrs)[3,6].
Open-ended questions**:** "describe in your own words the purpose of the study; "what more would you like to know?", "what is the possible benefit of participating in this study? “could you explain the possible risks?"

Closed-ended questions should not be asked: "do you understand?" "do you have any questions?"
"do you see that there are some risks to taking this drug?"
Participants should be allowed to decide:
do not coerce, convince or use undue influence to participate.

If a person is incompetent/incapable**,** consent must be obtained from the parent, legal guardian or legal representative in accordance with the law of the country. Research on vulnerable populations (Children, Institutionalized individuals - mentally challenged, old, prisoners, subordi- student/employee, military, tribal, uneducated ethnic minorities/refugees) not include unless study demands/ benefits special groups; consent are given from the individuals wherever possible[3,6]. For incapacitated participants, informed consent is signed by the legally authorised representative (LAR). Law defines who is qualified to be a LAR. Impartial witness required when the participant or the participant’s LAR is illiterate. A literate adult, independent of the research, cannot be unfairly influenced by people involved in the research. This person attends the informed consent process, attesting that consent is voluntary, freely given, and without any force or undue influence.

Agreement of local community leadership is good research practice/mandatory in some communities. There are obtained through a process of dialogue and often does not require written agreement. Agreement from the community leadership does not necessarily replace the consent and/or assent of individual participants. If no individual-level data are collected, in this case not require individual consent.

Informed consent is a process, not a onetime event of obtaining a signature. Information exchange between researcher and the potential participant starts before recruitment, continues throughout research project[6].

For ongoing discussion/interaction during study visits there should be understood some aspects: how is it documented, clear identification of the person who performed/ administered the informed consent, signed and dated by the participant and by the person who conducted the process in 2 forms and offer one copy to the participant and file the other. The role of the person taking consent are: communicate all information to prospective participant and answer queries; maintain confidentiality; avoid unjustified deception, undue influence, intimidation, false assurances, obtain written informed consent; witnessed/legal authorized representative as appropriate, assure that saying ‘no’ will not affect relationship/due benefits. There are some factors of informed consent insufficiency - participant factors (poor literacy rates, intimidation/stress, confusion about the consent process – doctors are ‘God’ and can make the decision); researcher factors (complex and lengthy forms, some notions are not easy to explain, like randomization, blinding, time limitations, wrong assumptions about participant understanding) [3,11].

Reasons of common discrepancies are: latest version of the informed consent form not used; several versions in use at a point in time; signatures not put at the appropriate place, copy not offered to the participant. Consent form dated later than the recruitment. They are not dated by investigator/ participants/ LAR/witness.

Regarding disclosure of information media also play role for better understanding of main aspects of informed consent. These media for disclosure of information are: audio-visual (video and audio material, photographs, pamphlets, advertisements, information on internet).

Questionnaires are frequently used survey instrument in research and comprises of a series of questions, designed to measure a given item or set of items. It may be self administered/by study site interviewers (face to face, telephone, mail, web-based).

Questions /study items and numbers must be kept as short as possible. The questions are simple, clear and unambiguous (without technical jargon); avoiding negative questions, hypothetical questions. Ordering and flow of questions should be logical, usually begin with socio-demographic questions.

Research proposals are subject to review by scientific committee prior to IRB/IEC submission: research question, study design and method, data analysis.

Ethics Committee most members have qualifications, expertise and experience to evaluate science, medical aspects etc. They are composed of at least 5 members –at least 1 member having no interest in scientific area, at least 1 member independent of institution/ study site.

Characteristics of a good ethics committee are multidisciplinary (scientific, medical, non-medical), multi sectorial (subject experts, biostatistician, legal experts, and religious head/theologian), community representatives (lay person, social scientist, and voluntary agencies) and are balanced distribution (age, gender, cultural background).

Review process implies reviewing the following documents: protocol/protocol amendments, participant information sheets, consent forms/updates, participant recruitment procedures (advertisements), investigator's CV, compensation for participants.

Review and approval is conducted before the initiation of the research. During the research any changes of the protocol and consent form could impact the risk benefit analysis andis subject to continuing review [7].

Ethical review is a holistic process; there are checked scientific design and conduct of the research, appropriate research design, valid methods, and recruitment of research participants, appropriate recruitment methods, care and protection of research participants.

Informed consent sample should provide complete information, should be understandable. It should be reviewing ethical concerns that safeguards vulnerable populations.
Physicians should consider the ethical, legal and regulatory norms and standards for involving human subjects in research in their own countries as well as applicable international norms and standards.

No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in Helsinki Declaration [11].

Investigator with regard to the research oversight committees should be aware of the requirements in the country and region, communication should have been - before, during and after the study safety and well being of research participants is paramount; review by competent and independent ethical committees is imperative, investigator is responsible to communicate with the applicable oversight committees. Research oversight is a quality check and provides public assurance of the ethics and quality of the study[1,6,7].

Privacy isa right of person to be protected. Confidentiality is about identifiable data. It is an agreement about maintenance access to identifiable data. It is important how to ensureprivacy and confidentialité (ddiscuss study in private area, if possible, use of codes and numbers as identifiers -no names; protection of records that could identify participant).

Personal information must be fairly and lawfully processed. It also must be processed in line with participant's rights and only for approved purpose and kept secure with access limited only to authorized study personnel, not kept for longer than is necessary and not transferred transferred to other countries without adequate protection[11].

For anonymizing data removing direct identifiers (name or address) are very useful; aggregating or reducing the precision of information or a variable, e.g. replacing date of birth by age groups, reducing precision of GPS coordinate; generalizing the meaning of detailed text, e.g. replacing a doctor's detailed area of medical expertise with an area of medical specialty; using pseudonyms; restricting the upper or lower ranges of a variable to hide outliers, e.g. top-coding salaries.

Quality in the context of clinical research includes several important aspects: conformance to standards, ensuring that the processes are reliable, procedures are complied, data generated are reliable, repeatable and auditable (traceable) [2].

Management of research projects include several aims:

- ◊ To ensure a common goal and clear definition of the project process. This process develops some questions, such are: what needs to be done? Whom? When?
- ◊ To enhance efficiency and timeliness;
- ◊ To promote teamwork;
- ◊ To allow systematic monitoring of study progress;
- ◊ To anticipate and address potential issues;
- ◊ To facilitate evaluation and development of reports.

Conclusion:

Components of a quality system include definition of roles and responsibilities, job descriptions and CVs, standard operating procedures/data collection guidelines. There are used different forms of quality system - document and version control, training records, field notes/lab notebook, facilities and equipment[2].

Quality assurance is planned and systematic actions that are established to ensure that the study is performed and the data are generated, recorded and reported in compliance with standards. Quality control act of overseeing ensures research is conducted, recorded and reported in accordance with protocol, SOP. There are reviewed: study documents, protocol, consents, data collection guidelines, processes and systems, personnel, SOPs/study guidelines, methods, data collection forms, database. Also there are measured study progressionon communication with team, milestones and activity timelines, work plan, used resources, cost and performance standards are reviewed.

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