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Ministry of Health
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Guidelines for Responsible Conduct of Clinical Studies and Trials

Centre of Studies and Research
Directorate General of Planning and Studies

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Foreword

Oman needs to continue to promote a strong culture of research and development in the health sector. However, attention needs to be paid to ensure that stringent quality checks are built in, and that researchers conduct research in an impeccable manner. Failure to do so will dent the credibility of the research enterprise, affecting not just researchers or health institutions conducting research, but also those planning to do so.

This is the first edition of the Guidelines for Responsible Conduct of Clinical Studies and Trials. The guideline advocates and describes the best practice in research for researchers and institutions, promotes integrity in research and explains what is expected from researchers, and assists researchers, administrators and the community on how to manage breaches from best research practice. It is addressed not only to researchers, but also to ethics review committees, investigational institutes, pharmaceutical manufacturers, sponsors of research drug regulatory authorities, the general public and those who have interest in clinical trials in Oman. This guideline not only serves the interests of the parties actively involved in the research process, but also protects the rights and safety of subjects, including patients, and ensures the investigations are directed to the advancement of public objectives of citizens.

This document provides information on how to manage research data and materials; ethics on how to publish and disseminate research findings (including proper attribution of authorship); obligations in peer review; and how to manage conflicts of interest. It is based on international standards but with an Islamic perspective and is a first time initiative by the Ministry of Health. Future revisions will take into consideration the evolving research guidelines and standards that are suitable to the situation and context in Oman.

I am confident that this guideline will help enhance research to meet high standards and assist institutions to better address allegations of misconduct in research

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Contents

List of Abbreviations

Abbreviation	Full term
ADR	Adverse Drug Reaction
CDBI	Comité Directeur pour La Bioéthique (Steering Committee on Bioethics, European Council)
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Record Form
DGPADC	Directorate General of Pharmaceutical Affairs and Drug Control
DSMB	Data Safety Monitoring Board
EC	Ethical Committee
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
IOMS	Islamic Organization for Medical Sciences
IRB	Institutional Review Board
PI	Principal Investigator
RERAC	Research and Ethical Review & Approve Committee
SAE	Serious Adverse Events
SOP	Standard Operating Procedure
WHO	World Health Organization
WMA	World Medical Association

Preface

The purpose of this document is to ensure that clinical studies that are conducted on human participants are designed and performed at the highest ethical and scientific standards. In conjunction with other published documents on this subject, this document will provide a positively oriented set of practical suggestions for maintaining integrity in research. Not only should the ethical conduct of research satisfy scientific, ethical and moral codes; it should also lead to better scientific results because the adherence to ethical research practices which lead to more attention to the details of scientific research, whether the study involves qualitative evaluation or quantitative analysis with statistical techniques or seeks more thoughtful collaboration among researchers. Also, the credibility of science with the general public depends on the maintenance of the highest ethical standards in research (1). Observance and compliance to this document will help researchers avoid deviating from accepted ethical research practices and prevent the more deviations that constitute research misconduct.

Research misconduct is defined as fabrication, falsification, or plagiarism, including misrepresentation of credentials, in proposing, performing, or reviewing research, or in reporting research results. It does not include honest error or differences of opinion. Misconduct as defined above is viewed as a serious professional deviation that is participant to sanctions imposed by institutions such as universities, by many professional associations, and, in the case of research proposed to or funded by a federal agency, by that agency (2).

The conduct of clinical research in accordance with the principles of Good Clinical Practice (GCP) helps to ensure that clinical research participants are not exposed to undue risk, and that data generated from the research are valid and accurate. By providing a basis both for the ethical and scientific integrity of research involving human participants and for generating valid observations and sound documentation of the findings, GCP not only serves the interests of the parties actively involved in the research process, but also protects the rights, safety and wellbeing of participants and ensures that investigations are scientifically sound and advance public health goals (1).

Introduction

The Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO) have developed international guidelines for biomedical research. Many countries and many organizations have evolved or adapted these concepts of biomedical research to suit their own loco-regional needs as well as societal and religious considerations. The Islamic Organization for Medical Sciences (IOMS) in Kuwait convened a meeting in Cairo, Egypt in 2004 and produced a document advancing an Islamic viewpoint on these principles and guidelines (3). This document and similar documents that are more specific to the Islamic view point are relevant to some of the research area (See appendix for details). The research committees in Oman take cognizance of all appropriate ethical principles in its perusal of research in Oman. The central Research and Ethical Review & Approve Committee (RERAC) oversee and is the ultimate authority for authorizing research conducted at the various health facilities including hospitals throughout the country.

Compliance to ethical issues in clinical research is of critical importance. Failure to adhere to ethical standards may not only lead to the loss of reputation of the researcher but can also lead to litigations as many issues pertaining to ethics are also legally binding. There are also issues related to the conduct of research which are considered professionally appropriate though they may not have legal consequences. These issues of professionalism in the conduct of research is termed here as the *etiquette in research*. For example, failure to voluntarily disclose a conflict of interest is more a matter of research etiquette than a cognizable ethical offence.

This document is a guideline that gives an overview of some of the ethical concepts and etiquette necessary in conducting clinical research and clinical trials. It is not intended to serve as a complete set of reference on ethical issues. The reader is advised to read additional information pertaining to any specific research component from available resources in published literature including online information from recognized and authentic websites for application in a proposed clinical research. Some important reference material is provided in the Appendices section of this document as well as in checklists.

In order to appreciate and apply concepts of ethics and etiquettes in clinical studies at various stages of research, the steps involved in clinical studies should be understood so that all relevant concepts can be applied at the corresponding stages in the study. Usually, the **genesis of a clinical study** would be at the point of identifying a clinical problem or a specific situation that needs to be explained or better defined. A thorough search for all available information on that topic should then be done after which an answerable question should be framed and a testable hypothesis defined. An appropriate study design that can optimally answer the research question should be identified and proceeded with. The population under consideration, the sample to be studied, any intervention if it is a clinical trial, safety and anonymity of all participants, duration of follow up, measurements of study variables, avoidance of bias, analysis and interpretation of results and dissemination of the study output are some of the important steps that would follow in a sequential order in most clinical studies. At every step there are ethical issues that will need attention. In the following chapters, most of the commonly occurring situations related to the planning, conduct and compilation of clinical studies and the ethical issues associated with each are described in some detail.

CHAPTER ONE:

Provision and Prerequisites for a Clinical Trial

1.1 Identifying a Clinical Problem

The need for clinical research invariably starts with the identification of a clinical problem or detection of an unexpected or unusual event or the need to explain in more detail an existing clinical situation or to develop a greater understanding of a clinical event or situation. Whether such an observation was an adverse event or a favourable event, it should not be ignored but further investigated through appropriate enquiry or research. The role of ethics requires that for the advancement of scientific knowledge (which in turn can improve health or minimize suffering), situations that can be studied should be subjected to an appropriate enquiry. Such a scientific enquiry, whether done by clinicians who encounter the situation or a researcher who works on that situation, will constitute a research. If the research is conducted on human participants it can be construed as clinical research. Such research can be through an experimental design where the researcher intervenes in a specified manner (Clinical Trial) or through an observational design in which the researcher observes a sequence of events prospectively or records events retrospectively without intervening in the process (Clinical Study).

1.2 Information Retrieval and Appraisal

Prior to conducting clinical research, the researcher is obliged to carry out an exhaustive search to identify and peruse all available and accessible information on the topic to be researched. Background information that gives a lead to the understanding of the situation and foreground information about the situation itself should be clearly understood by the researcher. If available literature on the situation clarifies the problem to be addressed, there is no further need to address that issue unless there is some lacunae in the understanding of the problem or some new information has since become available that warrants a review of the problem. It would be unethical to spend time, effort and resources to repeat research that has already been done. There is no need to "re-invent the wheel".

Often there is a tendency by researchers to only look at information that favours their point of view while ignoring published information that may contradict their idea. This leads to a biased

opinion on the situation that may generate a biased conclusion of the research and further invalidate a true understanding of the situation. The reader of a research and even policy makers may not be knowledgeable enough to critique research output and hence poor quality or inappropriate research may have adverse consequences. Though poor quality research may not tantamount to fraud, it is the responsibility of the researcher to ensure that all possible biases in the study are avoided as best as possible.

1.3 Framing an Answerable Research Question

In order to conduct research, a potentially answerable question has to be framed. Answers that are sought should attempt to resolve the identified clinical problem or provide more knowledge and information on it. If the information that is gathered will not contribute to the advancement of the knowledge base on the cited problem, the time, effort and money spent on it would be a waste. Also, if the information gathered may not lead to a benefit for the individual participant or even the society but may directly or indirectly harm the individual participant even something as apparently innocuous as an adverse labelling effect, **such research should be avoided**.

1.4 Formulating a Research Hypothesis

Every clinical research is actually testing a hypothesis. Even though it may not be specifically stated in every research proposal or protocol, there is always an implicit hypothesis. Even in the so called hypothesis generating studies the researcher is actually attempting to establish a fact whether the findings of the proposed research will generate observation that are consistent with certain expectations or not. A scientific hypothesis should be testable and even refutable. Hypotheses that may have a moral, spiritual or other unprovable component should be avoided as it would be ethically improper to frame such hypothesis.

1.5 Utilising an Appropriate Study Design

Every researcher must employ the best possible research design to answer the identified research problem. There are many instances where inferior study design has provided the wrong answer. Historically, there are many instances of useless or even harmful treatment that has been

promoted and propagated by well-meaning clinicians on patients because of published research that recommended such treatment were the result of poor study design. Hence, every researcher is ethically obliged to ensure that an appropriate study design is employed so that the conclusions and recommendations of the research are valid and reliable. There is a hierarchy of evidence in which the best available evidence is from a well conducted meta-analysis on that topic. In the absence of a meta-analysis, a Randomized Clinical Trial (RCT) would be the next best design especially when evaluating the effect of a clinical intervention. Since many clinical problems are not amenable to RCT because it is not feasible or for ethical reasons, an observational rather than an interventional study would only be feasible. Among observational studies, prospective studies are higher in the hierarchy in providing better evidence than retrospective or cross-sectional studies.

A. Observational Studies

In observational or descriptive studies, data is collected from the participant through direct or indirect observation or by voluntarily gathering information provided by the participant. Though superficially it may appear that there are no major ethical issues, there can arise serious ethical concerns in the utilisation of even voluntarily revealed information. Matters of anonymity, confidentiality, security of the provided information etc. has ethical overlay. On this matter the researcher may have access to personal information of a critical nature that may have a bearing or potential harm to the individual or the community. What should be done with such information has ethical consideration and hence has to be clearly addressed in the study protocol itself. It is equally important that only the information that are directly relevant to the research question should be elicited. It is a common mistake that personal or other information that are not directly relevant to the study and the hypothesis being tested are collected with the assumption that some association may show up on the variables collected. Gathering unnecessary personal data, even though they may be voluntarily obtained from the participants, is unethical.

B. Interventional Studies

All interventional studies are fraught with ethical issues, many of which are discussed in this document in various sections. The ethical concepts of beneficence, non-maleficence, justice and equity are most applicable in this situation. Of equal importance ethically is the control group, especially on matters of the use of placebo.

1.6 Selecting the Study Population

Based on the nature of the study and the level of existing knowledge, the study population could vary. For example, in a therapeutic trial of a drug, there are 4 levels of clinical trials ranging from assessment of tolerance, toxicity, efficacy, effectiveness and continuing on to Post marketing surveys. The population under consideration in this case will need to be the patients who require the medication under trial. It may also be necessary to include healthy volunteers in some cases. It is well documented historically that vulnerable population groups have been sometimes subjected to therapeutic trials in an unethical manner. Even recently, there are incriminating evidence that, loop holes in the rules and regulations of some developing countries have been exploited to run therapeutic trials in populations of those countries while the same research would not have been possible in developed countries (4-6). Such practice is certainly unethical and researchers should be aware of such situations and avoid them (7). The recommended application of the research findings in any study will always be limited to a population that resembles the study population. In most cases, the entire population of interest cannot be studied and hence an appropriate sample that represents the population closely will need to be studied.

1.7 Proper Sampling

Most studies involve a sample from the population of interest. A proper choice of the study sample such that it truly represents the study population is important, failing which the outcome of the study cannot be generalized to the parent population. A proper sampling technique and adequate sample size is critical to reduce selection bias and enhance the power of the study

(which should not be less than 80% in most studies). The researcher must specify and record the sampling technique. Failure to report the employed sampling process is an error that is seen frequently. Many instances of wrongly reporting the sampling process (such as stating that the sample was random when in fact, it was not truly so) are well known and such **declarations amount to fraud in research and not just a breach of research ethics**.

1.8 Maintaining and Following up After Intervention

Inadequate follow up after intervention, use of an unproven or inappropriate "proxy" outcome measure, incomplete follow up, loss to follow up etc. are common problems that happen in longitudinal and interventional studies. Truthfully recording and documenting all such problems and analysing them appropriately are ethical requirements.

1.9 Avoiding / Reducing Bias

Bias is defined as a systematic deviation from truth. Hence, the researcher must take every effort to avoid or at least reduce all potential bias in the study. Bias may occur at various stages in the study process from selective review of literature to interpretation of results. Among the more important bias that may commonly occur in clinical studies are selection bias and measurement bias. Methodological techniques like randomization, blinding, objective evaluation of outcomes etc. will reduce the potential for such bias.

1.10 Analysing and Managing Data

In recent years especially with the advent of computers, powerful statistical tools are available to the researchers to analyse and interpret the data obtained through clinical research. Appropriate use of statistical tests is important to make reasonable and justifiable conclusions. Data "dredging", data "tweaking" and such manipulations are often resorted to by researchers to prove a "point". Such practices, though may not amount to fraud is poor research etiquette as they can mislead the users of the research output.

1.11 Conclusion and Interpretation

The conclusion section of the research should confine to what has been achieved by the study and not extrapolate it to what could be achieved by the application of the study results. It is common to read many research publications where the stated conclusion exceeds the research objectives and the results obtained. Such inflated claims may mislead the clinician to overestimate the applicability of the study outcome in routine clinical practice.

1.12 Research Output

The complete process of writing up the completed research including the analysis and interpretation can be termed as the **research output**. There are several issues of ethics and etiquette that are applicable even at this stage and are highlighted in the following sections in more detail.

CHAPTER TWO:

Protection of Clinical Trial Participants

2.1 Declaration of Helsinki

The current revision of the Declaration of Helsinki (8) (Appendix 9) is the accepted basis for clinical trial ethics, and must be fully followed and respected by all parties involved in the conduct of such trials. Any deviations from the Declaration must be justified and stated in the protocol. Independent assurance that participants are protected can only be provided by an ethics committee and freely obtained informed consent.

2.2 Research and Ethics Committee

The role of the ethics committee (or other board responsible for reviewing the trial) (9) is to ensure the protection of the rights and welfare of human participants participating in clinical trials, as defined by the current revision of the Declaration of Helsinki and national and other relevant regulations, and to provide public reassurance, *inter alia*, by previewing trial protocols, etc.

A. Establishment of Research and Ethical Review & Approve Committee (RERAC)

Since 1998, the Clinical Research and Studies Committee which was under the Non-Communicable Diseases (NCD) Directorate had been reviewing and approving research in the Ministry of Health in Oman. In the 7th plan (2006-2010), the Directorate of Research and Studies revised and updated the rules and functions of the Committee and adopted new guidelines and forms for submission of proposals. The Research and Ethical Review & Approve Committee (RERAC) was promulgated by Ministerial Decision and was constituted on 23 February 2011 with a specific mandate and Terms of Reference. The Committee consists of members comprising statisticians, epidemiologists, health service providers, clinical researchers, information technology experts and specialists in bioethics. All of them are from the Ministry of Health (MoH), Sultan Qaboos University or the Oman Medical Specialty Board (OMSB). RERAC is a central committee in MoH and in addition, every region has its own Regional Research Committee that evaluates research and ethical issues related to research conducted in

their respective regions. They work in accordance with the guidelines laid down by central RERAC. In 2015, RERAC was reformed with new members along with a revised system of reviewing to meet the new process of online submission of research proposals.

B. Role of RERAC from an Ethical Point of View

RERAC is the central committee in the MoH and it is responsible for overseeing that all submitted protocols are in accordance with the research principles laid down by various international agencies and in particular the Helsinki Declaration of **WORLD MEDICAL ASSOCIATION (**WMA), the Good Clinical Research Practice laid down by WHO, Ethics of Clinical Research from an Islamic Perspective and similar recognized documents on Clinical Research Ethics. Every research proposal that is submitted to RERAC is reviewed using a checklist to ensure that strict ethical guidelines and appropriate research methodology are followed. Feedback is given to the Principal Researcher on the acceptability of the proposal. Those that do not meet the acceptable standards are rejected or disapproved. A copy of the checklist is attached in the Appendix for reference.

The roles of the RERAC are to:

1. Review research proposals from both scientific and ethical aspects in accordance with the accepted scientific rules and regulations
2. Participate in developing policies, regulations and plans that are required to conduct scientific and ethical research.
3. Approve rules, guidelines, research proposal forms, review mechanisms and provide researchers with them
4. Ensure that all clinical, epidemiological and other types of research are in accordance with the to the scientific and ethical rules and regulations of the Sultanate of Oman
5. Provide the regional research committees with rules, guidelines, research proposal forms, review mechanisms which are applied at RERAC

2.3 Informed Consent of Trial Participants

- In obtaining and documenting informed consent, the researcher should comply with the applicable regulatory requirement(s) as well as adherence to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the researcher should have the RERAC written approval of the written informed consent form and any other written information to be provided to the study participants (10, 11).
- The written informed consent form and any other written information to be provided to participants should be revised whenever important new information becomes available that may be relevant to the participant's consent.
- Any revised written informed consent form and written information should receive the RERAC approval in advance.
- The participant or the participant's legal representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of such information should be documented.
- Neither the researcher nor staff involved in the trial should coerce or unduly influence a participant to enrol or to continue to participate in a trial.
- None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the participant or the participant's legal representative to waive or to appear to waive any legal rights, or that releases or appears to release the researcher , the institution, the sponsor, or their agents from liability for negligence (10).
- The researcher, or a person designated by the researcher , should fully inform the participant or, if the participant is unable to provide informed consent, the participant's legal representative, of all pertinent aspects of the trial including the written information given approval/favourable opinion by the RERAC.

- The language used in the oral and written information about the trial, including the written informed consent form should be understandable to the participant or the participant's legal representative (10).
- Before informed consent is obtained, the researcher, or a person designated by the researcher, should provide the participant or the participant's legal representative ample time and opportunity to enquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the participant or the participant's legal representative (10).
- Prior to a participant's enrolment in the trial, the written informed consent form should be signed and personally dated by the participant or the participant's legal representative, and by the person who conducted the informed consent discussion (12).
- If a participant is unable to read or if a legal representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to participant is read and explained to the participant or the participant's legal representative, and after the participant or the participant's legal representative has orally consented to the participant's participation in the trial, and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the participant or the participant's legal representative, and that informed consent was freely given by participant or the participant's legal representative (10, 12).
- Both the informed consent discussion and the written informed consent form and any other written information to be provided to participants should include explanations of the following (10):
    - ***That the trial involves research.***
    - ***The purpose of the trial.***

- ***The trial treatment(s) and the probability for random assignment to each treatment.***
- ***The trial procedures to be followed, including all invasive procedures.***
- ***The subject's responsibilities.***
- ***Those aspects of the trial that are experimental.***
- ***The reasonably foreseeable risks or inconveniences to the participant and, when applicable, to an embryo, foetus, or nursing infant.***
- ***The reasonably expected benefits. When there is no intended clinical benefit to the subject, the participant should be made aware of this.***
- ***The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.***
- ***The compensation and/or treatment available to the participant in the event of trial-related injury.***
- ***The anticipated prorated payment, if any, to the participant for participating in the trial.***
- ***The anticipated expenses, if any, to the participant for participating in the trial.***
- ***That the subject's participation in the trial is voluntary and that the participant may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the participant is otherwise entitled.***
- ***That the monitor(s), the auditor(s), the RERAC will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the participant or the subject's legally acceptable representative is authorizing such access.***
- ***Those records identifying the participant will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.***

- ***That the participant or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.***
- ***The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.***
- ***The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.***
- ***The expected duration of the subject's participation in the trial.***
- ***The approximate number of participants involved in the trial.***

- Prior to participation in the trial, the participant or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the participant or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects (10).
- When a clinical trial (therapeutic or non-therapeutic) includes participants who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e. g. minors, or patients with severe dementia), the participant should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the participant should assent, sign and personally date the written informed consent.
- Except as described in (next point), a non-therapeutic trial (i. e. a trial in which there is no anticipated direct clinical benefit to the subject) should be conducted in participants who personally give consent and who sign and date the written informed consent form.
- Non-therapeutic trials may be conducted in participants with consent of a legally acceptable representative provided the following conditions are fulfilled (10):
    - ***The objectives of the trial cannot be met by means of a trial in participants who can give informed consent personally.***
    - ***The foreseeable risks to the participants are low.***
    - ***The negative impact on the subject's well-being is minimized and low.***

- ***The trial is not prohibited by law.***
- ***The approval of the RERAC is expressly sought on the inclusion of such subjects, and the written approval covers this aspect.***

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Participants in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

- In emergency situations, when prior consent of the participant is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the participant is not possible, and the subject's legally acceptable representative is not available, enrolment of the participant should require measures described in the protocol and/or elsewhere, with documented approval by the Institutional Review Board (IRB), to protect the rights, safety, and well-being of the participant and to ensure compliance with applicable regulatory requirements. The participant or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested (10).

2.4 Privacy and Confidentiality

The researcher must establish secure safeguards of confidentiality of research data as described in the current revision of the international ethical guidelines for biomedical research involving human subjects (13).

One of the conditions on which informed consent rests is that participants' privacy will be respected. Privacy refers to "persons and to their interest in controlling the access of others to themselves," and no participant should ever be forced to reveal information to the researcher that the participant does not wish to reveal. Confidentiality is equally important and refers to information about the person that has been revealed to the researcher. Especially in medical research, researchers are in a position of responsibility and dealing with a great deal of very personal information that their participants have agreed to disclose. Safeguarding this

information is a key part of the relationship of trust and respect that exists between the researcher and the participant. Depending on the type of study, personal identifiers such as names, birthdates, places of residence etc. may or may not have to be collected. In situations where these data are collected, researchers may take several steps to ensure the confidentiality of their participants' information, including (13, 14):

- Use participant codes to label data instead of using names, and keeping a separate list of code-to-name match-ups.
- In interview studies, use the participant's first name only (or even using an alias) when recording or publishing data. Most of the time, an alias will suffice, and is especially important to protect the participant if the published data includes other identifiers such as age, gender, community affiliations, or place of residence.
- Be careful not to publish enough information that the participant can be identified.

CHAPTER THREE:

Ethics of Research Publication

3.1 Plagiarism

Authors who present the words, data, or ideas of others with the implication that they are their own, without attribution in a form appropriate for the medium of presentation, are committing theft of intellectual property and may be guilty of plagiarism and thus of research misconduct (15).

An author should cite the work of others even if he or she had been a co-author or editor of the work to be cited or had been an adviser or student of the author of such work, whether published or unpublished and whether it had been written work, an oral presentation, or material on a website (2).

3.2 Misuse of Privileged Information

One particularly serious form of plagiarism is the misuse of privileged information taken from a grant application or manuscript received from a funding agency or journal editor for peer review, because it not only deprives the original author of appropriate credit by citation but could also pre-empt priority of first publication or use of the original idea to which the source author is entitled. Also, one who breaches confidentiality by showing a privileged unpublished document to an unauthorized person can be held to a shared responsibility for any subsequent plagiarism of the document committed by that unauthorized person (2).

3.3 Data

A. Integrity of Data

Fabrication and falsification of research results are serious forms of misconduct. It is the primary responsibility of a researcher to avoid either a false statement or an omission that distorts the research record. In order to preserve accurate documentation of observed facts with which later reports or conclusions can be compared, every researcher has an obligation to maintain a clear and complete record of data acquired. These records should include sufficient detail to permit

examination for the purpose of replicating the research, responding to questions that may result from unintentional error or misinterpretation, establishing authenticity of the records, and confirming the validity of the conclusions (2, 13).

B. Use and Misuse of Data

Research integrity requires not only that the reported conclusions are based on accurately recorded data or observations but also that all relevant observations are reported. It is considered a breach of research integrity to fail to report data that contradict or merely fail to support the reported conclusions, including the purposeful withholding of information about confounding factors. If some data should be disregarded for a stated reason, confirmed by an approved statistical test for neglecting outliers, the reason should be stated in the published accounts (2).

C. Ownership of and Access to Data

Research data obtained in studies performed at an institution are not the property of the researcher who generated or observed them or even of the principal researcher of the research group. They belong to the institution it was conducted in, which can be held accountable for the integrity of the data even if the researchers have left that institution (16).

A principal investigator (PI) who leaves an institution is entitled to make a copy of data to take to another institution so as to be able to continue the research or, in some cases, to take the original data, with a written agreement to make them available to the original institution on request within a stated time period. A formal Agreement on Disposition of Research Data should be negotiated in such situations including the division of research materials e. g. specimens etc. (2).

D. Storage and Retention of Data

Data should be stored securely for at least 3 years after completion of the project, submission of the final report to a sponsoring agency, or publication of the research, whichever comes last (2).

E. Interference

A research misconduct is improper withholding of data and intentional removal of, interference with, or damage to any research-related property, including instruments and other equipment (2).

3.4 Authorship and other Publication Issues

It is an ethical obligation for a researcher to publish research results in a timely manner so as to communicate it to the scholarly world so that other researchers may build on the reported findings. The reported data and methods should be sufficiently detailed so that other researchers could attempt to replicate the results.

A commercial sponsor of a research project may not have a veto over a decision to publish, but a delay of publication for an agreed period, not to exceed six months, may be allowed in order to permit filing of a patent application (2, 17).

A. Criteria for Authorship

Publication must give appropriate credit to all authors for their roles in the research. If more than one person contributes significantly, the decision of which names are to be listed as co-authors should reflect the relative contributions of various participants in the research. Many professional associations and research journals have specified criteria for authorship. One common standard appearing in many of these statements is that each author should have participated in formulating the research problem, interpreting the results, and writing the research paper, and should be prepared to defend the publication against criticisms. A person's name should not be listed as author without his or her knowledge, permission, and review of the final version of the manuscript that includes the names of all co-authors (2, 17).

A person whose contribution merits co-authorship should be named even in oral presentations, especially when abstracts or transactions of the proceedings of a conference at which a paper is presented will be published. The entitlement to authorship should be the same whether or not a person is still at the original location of the research when a paper is submitted for publication.

Just as one should include all those who have a right to be listed as co-authors, so one should avoid the listing of so-called honorary authors, who do not meet the criteria for authorship (16). Many published versions of standards for authorship suggest the use of alternative forms of acknowledgment within the paper for contributions that do not merit co-authorship, e. g. , for technical assistance, for providing research materials or facilities, or for meeting some but not all of the stated criteria for authorship. To avoid misunderstandings and even recriminations, the inclusion and exclusion of names of research participants as co-authors should be made clear to all participants in the research prior to submission of the manuscript (2).

B. Order of Authors

Customs regarding the order in which co-authors' names appear vary with the discipline. Whatever the discipline, it is important that all co-authors understand the basis for assigning an order of names and agree in advance to the assignments (16, 18).

A corresponding, or senior author (usually the first or last of the listed names in a multi-authored manuscript) should be designated for every paper, who will be responsible for communicating with the publisher or editor, for informing all co-authors of the status of review and publication, and for ensuring that all listed authors have approved the submitted version of the manuscript. This person has a greater responsibility than other co-authors to vouch for the integrity of the research report and should make every effort to understand and defend every element of the reported research (2, 15).

C. Self-citations

In citing one's own unpublished work, an author must be careful not to imply an unwarranted status of a manuscript. A paper should not be listed as submitted, in anticipation of expected submission. A paper should not be listed as accepted for publication or in press unless the author has received galley proof or page proof or has received a letter from an editor or publisher stating that publication has been approved, participant perhaps only to copy-editing (2).

D. Duplicate Publication

Researchers should not publish the same article in two different places without very good reason to do so, unless appropriate citation is made in the later publication to the earlier one, and unless the editor is explicitly informed. The same rule applies to abstracts. If there is unexplained duplication of publication without citation, sometimes referred to as self-plagiarism, a reader may be deceived as to the amount of original research data (2, 15).

It is improper in most fields to allow the same manuscript to be under review by more than one journal at the same time. Very often journals specify that a submitted work should not have been published or submitted for publication elsewhere, and some journals require that a submitted manuscript be accompanied by a statement to that effect.

An author should not divide a research paper that is a self-contained integral whole into a number of smaller papers merely for the sake of expanding the number of items in the author's bibliography.

Publication of two papers representing different interpretations of the same data by different participants in the research is confusing to readers. The participants with differing interpretations of the same data should attempt to reconcile their differences in a single publication or present their alternative interpretations in the same paper (2, 18).

E. Early Release of Information Prior to Publication

It is unethical to release to the media scientific information contained in an accepted manuscript prior to the publication. An exception may be made if a public health issue is involved and the editor agrees to an advance release (2).

3.5 Obligation to Report

A. Reporting Suspected Misconduct

Reporting suspected research misconduct is a shared and serious responsibility of all members of the research team. Any person who suspects research misconduct has an obligation to report the allegation to the central committee (2, 15).

B. Correction of Errors

If a finding of error, either intentional or inadvertent, or of plagiarism should be made subsequent to publication, the researcher has an obligation to submit a correction or retraction in a form specified by the editor or publisher (2).

3.6 Conflict of Interest

There are some circumstances in which conflicts of interest could compromise the integrity of research or even lead to research misconduct, for example, by the distortion of research outcomes as a result of personal financial interests of a researcher. A notice of conflicting financial interests must be included (18). Many journals and funding agencies require such disclosures. When asked to enter into peer review of a manuscript or proposal, a researcher must disclose any conflict of interest with respect to the matter under review (2, 17).

3.7 Joining International Studies

When joining international studies, ethical considerations need to be evaluated and in the context of Oman. The consent should be in a language understood by the layperson taking into consideration local terminologies. The data collected should be protected and ownership identified clearly in the application stating the accessibility of the data and the authorship and protection of rights of researchers involved, including citations for the various levels of data.

CHAPTER FOUR:

Responsibilities of the Investigator and the Investigational Institution

4.1 Qualifications of the Researcher and Agreements

The researchers should:

- Have sufficient qualifications (education, training and experience) recognized by the Sultanate of Oman.
- Have good knowledge of and experience in the field of study defined by the protocol.
- Be competent in the field of study as evidenced by an updated curriculum vitae.
- Be competent and experienced in research or receive scientific support from experienced colleague(s).
- Have the necessary capabilities to participate in and take full responsibility for the proper conduct of the study.
- Be thoroughly familiar with and be qualified for the appropriate use of the investigational product(s)/materials, as described in the protocol.
- Be aware of, and comply with the RERAC guidelines and the applicable regulatory requirements.
- Permit monitoring, auditing and inspection by the Centre of Studies and Research staff.

4.2 Medical Care of Clinical Trial Participants

- A qualified physician, who is a principal investigator or a co-investigator of the trial, should be responsible for all trial-related clinical decisions.
- During and following a subject's participation in a trial, the investigational institution should ensure that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the trial. The investigational institution should inform a participant when medical care is needed for intercurrent illness(es) of which the researcher becomes aware.
- Although a participant is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the researcher should make a reasonable effort to ascertain the reason(s), while fully respecting the participants' rights (10, 12).

4.3 Compliance with Protocol

- The investigational institution should assure that conduct of trial is in compliance with the protocol which was agreed to by the sponsor and given approval by the RERAC.
- The researcher should not implement any changes in the protocol without agreement by the sponsor and prior review and approval from the RERAC, with the following exceptions:
  - ***To eliminate an immediate hazard(s) to trial participants. The implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted to RERAC as soon as possible.***
  - ***Minor change(s) involves only logistical or administrative aspects of the trial (e. g., change of monitor(s), change of telephone number(s)), to be included in periodical report to RERAC.***
- The researcher, or person designated by the researcher, should document and explain any deviation from the approved protocol (10, 12).

4.4 Investigational Product(s)

- The investigational institution is responsible about the accountability of the investigational product(s) at the trial site(s).
- The investigational institution may assign some or all of the researcher's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate researcher or another appropriate individual who is under the supervision of the investigational institution.
- The investigational institution and/or or other appropriate individual, who is designated by the investigational institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each participant , and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Researchers

should maintain records that document adequately that the participants were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor (10).

- The investigational product(s) should be stored as specified by the sponsor and in accordance with applicable regulatory requirement(s).
- The researcher should ensure that the investigational product(s) are used only in accordance with the approved protocol (19).
- The researcher , or a person designated by the investigational institution, should explain the correct use of the investigational product(s) to each participant and should check, at intervals appropriate for the trial, that each participant is following the instructions properly (10, 17).

4.5 Randomization Procedures and Un-blinding

The researcher should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the researcher should promptly document and explain to the sponsor any premature un-blinding (e.g. accidental un-blinding, un-blinding due to a serious adverse event) of the investigational product(s) (10, 12).

4.6 Records and Reports

- The researcher should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the Case Record Form (CRF) and in all required reports.
- Data reported on the CRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.
- Any change or correction to a CRF should be dated, initialled, and explained (if necessary) and should not obscure the original entry (i.e. an audit trial should be maintained); this applies to both written and electronic changes and corrections. Sponsors should provide guidance to researchers and/or the researchers' designated representatives on making such corrections. Sponsors should have written procedures to assure that

changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the researcher. The researcher should retain records of the changes and corrections (10).

- The investigational institution should maintain the trial documents. The investigational institution should take measures to prevent accidental or premature destruction of these documents.
- Documents should be retained until at least 3 years or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. In this case it is the responsibility of the sponsor to inform the investigational institution as to when these documents no longer need to be retained (10).
- The financial aspects of the trial should be documented in an agreement between the sponsor and the investigational institution.
- Upon request of the monitor, auditor or RERAC, the investigational institution should make available for direct access all requested trial-related records.

4.7 Safety Reporting

- All Serious Adverse Events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g. investigational product brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify participants by unique code numbers assigned to the trial participants rather than by the participants' names, personal identification numbers, and/or addresses (10, 12). The researcher must also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the Directorate General of Pharmaceutical Affairs & Drug Control (DGPADC) and the RERAC.

- Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol (12).
- For reported deaths, the researcher should supply the sponsor and the RERAC with any additional requested information (e.g. autopsy reports and terminal medical reports).

4.8 Premature Termination or Suspension of a Trial

There can be several justifiable reasons for prematurely terminating a clinical trial. If such a situation can be anticipated prior to starting the study, the reasons and process for premature termination should be specified in the research protocol. For e. g. : If an interim analysis of a clinical trial shows that the undue benefit (or harm) in one of the treatment arms is significantly higher (or lower), the study may be terminated and the results disclosed for the benefit of all concerned (11). (In such cases, the statistical level of significance is set at a higher level to reduce chance alpha error in the interim stage). So also an interim analysis, which was not pre-planned, may be necessitated if undue benefit (or risk) is observed in any of the study groups. There may also be other unexpected and unplanned reason for discontinuation such as new information on the toxicology of a medication being used in the study, therapeutic benefit of an intervention, introduction of a superior agent during the study period, availability of a better diagnostic test etc. There may also be other reasons that may necessitate the discontinuation or suspension of a research project.

- If the trial is terminated prematurely or suspended for any reason, investigational institution should (10):
  - ***Promptly inform the trial participants.***
  - ***Assure appropriate therapy and follow-up for the participants, and,***
  - ***Inform the RERAC.***
- If the researcher terminates or suspends a trial without prior agreement of the sponsor, the researcher should inform the institution and RERAC and should provide a detailed written explanation of the termination or suspension.

- If the sponsor terminates or suspends a trial, the researcher should promptly inform the institution and RERAC and provide a detailed written explanation of the termination or suspension (10).
- If RERAC terminates or suspends its approval of a trial, the researcher should inform the investigational institution. The latter, should promptly notify the sponsor forwarding the detailed written explanation of the termination or suspension from RERAC.

4.9 Final Report(s) by Investigational Institution

Whether the trial is completed or prematurely terminated, the sponsor and Researcher should ensure that the clinical trial/study reports are prepared and provided to the RERAC.

CHAPTER FIVE:

Responsibilities of the Sponsor

5.1 Quality Assurance and Quality Control

- The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs) to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s) (10, 20).
- When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should (10):
  - ***Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i. e., validation).***
  - ***Maintain SOPs for using these systems.***
  - ***Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i. e., maintain an audit trial, data trial, etc.).***
  - ***Maintain a security system that prevents unauthorized access to the data.***
  - ***Maintain a list of the individuals who are authorized to make data changes.***
  - ***Maintain adequate backup of the data.***
  - ***Safeguard the blinding, if any (e. g., maintain the blinding during data entry and processing).***
- The sponsor should obtain the researcher 's/institution's agreement:
  - ***To conduct the trial in compliance with GCP, with the applicable regulatory requirement(s), and with the protocol agreed to by the sponsor and given approval by the RERAC.***
  - ***To comply with procedures for data recording/reporting: and***
  - ***To permit monitoring, auditing, and inspection.***

- ***To retain the essential documents that should be in the investigational institution files until the sponsor informs the investigational institution these documents are no longer needed.***

5.2 Compensation to Participants and Researchers

- If applicable, the sponsor should provide insurance or should indemnify (legal and financial coverage) the researcher /the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence (10).
- The sponsor's policies and procedures should address the costs of treatment of trial participants in the event of trial-related injuries in accordance with the applicable regulatory requirement(s) (11).
- When trial participants receive compensation, the method and manner of compensation should be as per MoH rules and guidelines.

5.3 Information on Investigational Product(s)

- When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.
- The sponsor should update the Investigational product brochure as significant new Information becomes available (10).

5.4 Manufacturing, Packaging, Labelling and Coding Investigational Product

- The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with all GMP guidance, and is coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory requirement(s) (10, 21).
- The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g., protection from light), storage times, reconstitution

fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g., monitors, researchers, pharmacists, storage managers) of these determinants (22).

- The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage (22).
- In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.
- If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g., stability, dissolution rate, and bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials (10).

5.5 Supplying and Handling Investigational Product(s)

- The sponsor is responsible for supplying the researcher(s)/institution(s) with the investigational product(s) (21).
- The sponsor should not supply an investigational institution with the investigational product(s) until the sponsor obtains all required documentation (8) (e.g., approval from RERAC and DGPADC.
- The sponsor should ensure that written procedures include instructions that the investigational institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)) (10).
- The sponsor should:

- ***Ensure timely delivery of investigational product(s) to the researcher(s).***
- ***Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s).***
- ***Maintain a system for retrieving investigational products and documenting this retrieval (e.g., for deficient product recall, reclaim after trial completion, expired product reclaim).***
- ***Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.***
- ***Take steps to ensure that the investigational product(s) are stable over the period of use.***
- ***Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.***

5.6 Record Access

The sponsor should verify that each participant has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, RERAC review, and regulatory inspection.

5.7 Safety Information

- The sponsor is responsible for the on-going safety evaluation of the investigational product(s).
- The sponsor should promptly notify all concerned researcher(s)/ institution(s) and the RERAC of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the RERAC approval to continue the trial.

5.8 Adverse Drug Reaction Reporting

- The sponsor should expedite the reporting to all concerned researcher(s)/institutions(s), and RERAC, and to the DGPADC of all Adverse Drug Reactions (ADRs) that are both serious and unexpected.
- Such expedited reports should comply with the applicable regulatory requirement(s) (23).
- The sponsor should submit to the Drug Control Department all safety updates and periodic reports, as required by applicable regulatory requirement(s) (10).

CHAPTER SIX:

Documents and Requirements for Clinical Studies and Trials

6.1 Table of Documents Required to be Submitted to Central RERAC for Approval of Clinical Trials

	Title of Document	Purpose/detail
1.	MoH's Form **A1**	A mandatory requirement of RERAC
2.	Declaration of conflict of interest for all researchers	
3.	Insurance contract with local insurance company (Not yet available in Oman)	To document that compensation to subject(s) for trial-related injury will be available
4.	Good Manufacturing Practice (GMP) certificates for the manufacturing site if the investigational drug not registered in Oman	To ensure that the investigational drug is manufactured as per acceptable international standards
5.	Good Laboratory Practice (GLP) Certificate (if required) "For tests performed outside MoH certified laboratories"	To ensure that the investigational test is performed in an internationally acceptable standard
6.	No Objection letter from sites where the trial will take place	To ensure the site where the clinical trial will be conducted is aware and agrees to participate if approved
7.	Consent form	Complying with RERAC standards In English and Arabic
8.	Patient information leaflets	In English and Arabic
9.	Any other Material/Adverts about the trial	If used
10.	CVs of all researchers	
11.	Sample of label(s) to be attached to all investigational product(s) and/or trial-related materials	To be stated clearly "for investigational purposes, not for sale" in English and Arabic

12.	Instructions of handling ,storage, reconstitution and dispensing of the investigational product(s) and/or trial- related materials	
13.	Certificate of analysis of drug content	To document identity, purity and strength of investigational product. This may require Halal certificate for animal source products.
14.	Shipping records for investigational product(s) and trial- related materials	To document shipment dates, Batch numbers, and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability.
15.	Signed ADR Reporting Declaration	The principal researcher will be held accountable to forward all ADR to Directorate General of Pharmaceutical Affairs & Drug Control within 15 working days of a minor incident or 2 working days of a major incident
16.	Normal value(s)/range(s) for medical/ laboratory/ technical procedure(s) and/or test(s) included in the protocol	To document normal values and/ or ranges of the tests
17.	Financial aspects of the trial	To document the financial agreement between the researcher /institution and/or the sponsor for the trial
18.	Sample of CRF	Case Report Form

19.	Amendment Declaration form	Declaration from the PI to submit to the central committee (RERAC) any amendments to the protocol or amendments to any previously submitted documents
20.	Decoding procedure for blinded trial	To state how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects
21.	**Additional requirements for International multicentre trials**	
	21. 1 Original protocol	
	21. 2 Original consent form	In English and if available in Arabic
	21. 3 Customized consent form (if needed)	In English and Arabic
	21.4 List of the countries where the study is submitted and it status (Approved/Pending/Rejected)	
	21.5 Signed agreement between all parties involved in the trial, e. g. -Researcher /institution and sponsor -Researcher /institution	

After fulfilment of the above requirements, RERAC will give the final decision in 1-2 months. Note that failure to submit required documents will result in further delay. Once the preliminary approval is granted, the primary researcher must submit to RERAC a document stating that the site is suitable and ready to conduct the trial and that all necessary training has been completed. This is to ensure that the trial will be conducted as designed. The final approval will be granted within 2 weeks of receiving this document.

6.2 Documents Required During the Clinical Conduct of the Trial

RERAC requires periodical reports during the clinical trials (every 6 months if the duration of the study is more than a year and every 3 months for trials less than a year)

These reports should include the following:-

Table of documents required to be submitted to Central Research Committee (RERAC) during the clinical conduct of the trials.

	Title of Document	Purpose/detail
1.	Accrual summary	Including list of pre-trial screened, eligible and recruited participants
2.	Copies of Signed consent	
3.	Copies of reported ADR	Which should have already been forwarded to Directorate General of Pharmaceutical Affairs & Drug Control
4.	Relevant communications	Any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting.

6.3 Other Documents which are Required During the Clinical Conduct of the Trial

In addition to having on file the above documents in the previous 2 tables (Section 6.1 and Section 6.2), the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available.

	Title of Document	Purpose/detail
1.	Signed CRF forms	
2.	Subjects' ID code list, if blinded	To permit identification of all participants enrolled in the trial in case follow-up is required.

3.	Investigational product(s) accountability at the site	To document that investigational products(s) have been used according to the protocol
4.	Tissue banking data when possible	To document location and identification of retained samples if assays need to be repeated
5.	Master Randomization List	

Please note that there will be periodical Audits at any time during the trial and the above documents may be requested.

6.4 The Required Documents by the End of the Trial

Upon completion or termination of the trial, the following are required to be reported to RERAC:

	Title of Document	**Purpose/detail**
1.	Documentation of investigational product(s) destruction	To document destruction of unused investigational product(s) by sponsor or at site
2.	Completed participant identification code list	To permit identification of all participants enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed-upon time
3.	Final trial close-out monitoring report	To document that all activities required for trial close-out are completed, and copies of essential document are held in the appropriate files
4.	Treatment allocation and decoding documentation	To document any decoding that may have occurred
5.	Final report by researcher	To document completion of the trial
6.	Clinical study report	To document results and interpretation of trial

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Appendices

Appendix 1: Glossary of Terms

Few important terms that are used in this document are briefly defined below as per standard definition given in the references that are cited.

Investigator / Researcher:

The qualified scientist who undertakes the scientific, legal and ethical responsibilities of the research that he/she conducts by himself/herself or on behalf of an organization or sponsor. He/she is also the leader of the team of co-researcher(s).

Research Protocol:

A written document that provides the background information of the research topic, justification for the research, stated aims and objectives of the study, describes the design and methodology of the research, specifies the recruitment, allocation and maintenance of the participants, management of the data generated and also specifies the role and responsibility of the members of the research team. Unlike a guideline, protocols have to be strictly adhered to and any deviation should be with due notification or authorization. Protocol may be amended according a specific need / situation / participant characteristic or to meet a situation that may arise in the course of the research but they must be done by the researcher / research team and which should be made known in writing to all concerned including the sponsor, supervisor and RERAC.

Standard Operating Procedure (SOP):

A written, well described document that states explicitly the steps to be followed in the conduct of a specific task, objective or procedure.

Beneficence:

This refers to the ethical obligation to maximize benefit and to minimize harm. This principle gives rise to norms requiring that the risks of research be reasonable in the light of the expected benefits, that the research design be sound, and that the researchers be competent both to conduct

the research and to safeguard the welfare of the research subjects.

Non-Maleficence:

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to other.

Justice:

The principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects. (The Belmont Report) Justice in the selection of research participants requires attention in two respects: the individual and the social.

Research Participant:

An individual who participates (as a subject) in a biomedical research project, either as the direct recipient of an intervention (e.g., study product or invasive procedure), as a control, or through observation. The individual may be a healthy person who volunteers to participate in the research, or a person with a condition unrelated to the research carried out who volunteers to participate, or a person (usually a patient) whose condition is relevant to the use of the study product or questions being investigated.

Randomization:

The process of allocation of the participant to the intervention is by a pre-determined probability or chance. This is to reduce potential for selection bias. Normally, consent to participate in the research should be obtained from every participant prior to randomization. Withdrawal from the intervention and dropouts after randomization should be minimal. Hence a clear understanding of the randomization process for allocation should be clearly explained to the participant through the consenting procedure.

Blinding / Masking:

Though the terms are not necessarily interchangeable, it refers to the situation where either the participant, the evaluator or the adjudicator or all three are unaware of the intervention imparted to the participant. This is done to reduce the potential for the outcome measurement bias. Ethical issues may be involved in blinding and the research proposal should clearly identify the need and justification for blinding.

Unblinding:

The process of revealing the intervention that was previously unknown through the blinding process. This may be intentionally done to ensure safety of the participant in order to provide management in the event of an adverse event. Unblinding becomes ethically mandatory in such instances. Such need for unblinding must be specified in the protocol. Unblinding may also happen unintentionally and it is the responsibility of the researcher to ensure that such situation does not happen. Recording if unintentional unblinding has occurred in a study is worth noting as it will identify potential for measurement bias.

Sponsor:

An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a research project. A pharmaceutical company, manufacturer of biomedical products often sponsor research to promote their product.

Conflict of Interest:

A situation where a researcher, member of a committee or any individual has the potential to favourably report on a product or event or situation. It may arise when the person has financial, material, institutional or social ties to the research.

Plagiarism:

To make a statement or declaration as if it is one's own when in fact it has been copied from a

previously existing or published statement but without acknowledging the original source of that statement. Information that is general knowledge in the public domain or what is in common usage in the profession need not be acknowledged.

Privileged Information:

Information of a special nature that has not been formally published as yet that an individual may get to know because of the role or responsibility of that individual as a reviewer, editor, sponsor, member of a research or funding committee or any such privileged position is termed as privileged information.

Appendix 2: Checklist of Documents Required to be Submitted to Central Research Committee (RERAC) for Approval of a Clinical Trial

	Title of Document	Yes	No	N/A
1.	Filled MoH's form specialized for clinical trials			
2.	Declaration of conflict of interest for all researchers			
3.	Insurance contract with local insurance company			
4.	Good Manufacturing Practice (GMP) certificates for the manufacturing site if the investigational drug not registered in Oman			
5.	Good Laboratory Practice (GLP) Certificate (if required) "For tests performed outside MOH certified laboratories"			
6.	No objection letter from the institution where the trial will take place			
7.	Consent form			
8.	Patient information leaflets			
9.	Any other Material/Adverts about the trial			
10.	CVs of all researchers			
11.	Sample of label(s) to be attached to all investigational product(s) and/or trial-related materials			
12.	Instructions of handling ,storage, reconstitution and dispensing of the investigational product(s) and/or trial- related materials			
13.	Certificate of analysis of drug content			
14.	Shipping records for investigational product(s) and trial- related materials where applicable			
15.	Signed ADR Reporting Declaration			
16.	Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol			
17.	Financial aspects of the trial			

18.	Sample of CRF			
19.	Amendment Declaration form			
20.	Decoding procedure for blinded trial			
21.	Original protocol			
22.	Original consent form			
23.	Customized consent form (if needed)			
24.	List of the countries where the study is submitted and it status (Approved/Pending/Rejected)			
25.	Signed agreement between all parties involved in the trial, e. g. -Researcher /institution and sponsor -Researcher /institution			
26.	Budget			
27.	Source of funding			

Appendix 3: Checklist of Documents Required to be Submitted to Central Research Committee (RERAC) During the Clinical Conduct of the Trial

	Title of Document	Yes	No	N/A
1.	Accrual summary			
2.	Copies of Signed consent			
3.	Copies of reported ADR			
4.	Statement of expense and budget utilization			

Appendix 4: Checklist of Extra Documents to be Added During the Trial

(As evidence that all new relevant information is documented as it becomes available)

	Title of Document	Yes	No	N/A
1.	Signed CRF forms			
2.	Subjects' ID code list, if blinded			
3.	Investigational product(s) accountability at the site			
4.	Tissue banking data when possible			
5.	Master Randomization List			

Appendix 5: Checklist of Documents to be Submitted to RERAC upon Completion or Termination of the Trial

	Title of Document	Yes	No	N/A
1.	Documentation of investigational product(s) destruction			
2.	Completed participant identification code list			
3.	Final trial close-out monitoring report			
4.	Treatment allocation and decoding documentation			
5.	Final report by researcher			
6.	Clinical study report			
7.	Balance sheet of accounts/ financial statement			

Appendix 6: Elements of the Review Process (Operational Guidelines for Ethics Committees that Review Biomedical Research)

Citation: *World Health Organization. Operational guidelines for ethics committees that review biomedical research; 2000. Available from: http://www. who. int/tdr/publications/training-guideline-publications/operational-guidelines-ethics-biomedical-research/en/(page 10-13).*

The primary task of an Ethics Committee (EC) lies in the review of research proposals and their supporting documents, with special attention given to the informed consent process, documentation, and the suitability and feasibility of the protocol. ECs need to take into account prior scientific reviews, if any, and the requirements of applicable laws and regulations.

The following should be considered, as applicable:

6.2.1 Scientific Design and Conduct of the Study

6.2.1.1 The appropriateness of the study design in relation to the objectives of the study, the statistical methodology (including sample size calculation), and the potential for reaching sound conclusions with the smallest number of research participants;

6.2.1.2 The justification of predictable risks and inconveniences weighed against the anticipated benefits for the research participants and the concerned communities;

6.2.1.3 The justification for the use of control arms;

6.2.1.4 Criteria for prematurely withdrawing research participants;

6.2.1.5 Criteria for suspending or terminating the research as a whole;

6.2.1.6 The adequacy of provisions made for monitoring and auditing the conduct of the research, including the constitution of a Data Safety Monitoring Board (DSMB);

6.2.1.7 The adequacy of the site, including the supporting staff, available facilities, and emergency procedures;

6.2.1.8 The manner in which the results of the research will be reported and published;

6.2.2 Recruitment of Research Participants

6.2.2.1 The characteristics of the population from which the research participants will be drawn (including gender, age, literacy, culture, economic status, and ethnicity);

6.2.2.2 The means by which initial contact and recruitment is to be conducted;

6.2.2.3 The means by which full information is to be conveyed to potential research participants or their representatives;

6.2.2.4 Inclusion criteria for research participants;

6.2.2.5 Exclusion criteria for research participants;

6.2.3 Care and Protection of Research Participants

6.2.3.1 The suitability of the researcher (s)'s qualifications and experience for the proposed study;

6.2.3.2 Any plans to withdraw or withhold standard therapies for the purpose of the research, and the justification for such action;

6.2.3.3 The medical care to be provided to research participants during and after the course of the research;

6.2.3.4 The adequacy of medical supervision and psycho-social support for the research participants;

6.2.3.5 Steps to be taken if research participants voluntarily withdraw during the course of the research;

6.2.3.6 The criteria for extended access to, the emergency use of, and/or the compassionate use of study products;

6.2.3.7 The arrangements, if appropriate, for informing the research participant's general practitioner (family doctor), including procedures for seeking the participant's consent to do so;

6.2.3.8 A description of any plans to make the study product available to the research participants following the research;

6.2.3.9 A description of any financial costs to research participants;

6.2.3.10 the rewards and compensations for research participants (including money, services, and/or gifts);

6.2.3.11 the provisions for compensation/treatment in the case of the injury/disability/death of a research participant attributable to participation in the research;

6.2.3.12 the insurance and indemnity arrangements;

6.2.4 Protection of Research Participant Confidentiality

6.2.4.1 A description of the persons who will have access to personal data of the research participants, including medical records and biological samples;

6.2.4.2 The measures taken to ensure the confidentiality and security of personal information concerning research participants;

6.2.5 Informed Consent Process

6.2.5.1 A full description of the process for obtaining informed consent, including the identification of those responsible for obtaining consent;

6.2.5.2 The adequacy, completeness, and understandability of written and oral information to be given to the research participants, and, when appropriate, their legally acceptable representative(s);

6.2.5.3 Clear justification for the intention to include in the research individuals who cannot consent, and a full account of the arrangements for obtaining consent or authorization for the participation of such individuals;

6.2.5.4 Assurances that research participants will receive information that becomes available during the course of the research relevant to their participation (including their rights, safety, and well-being);

6.2.5.5 The provisions made for receiving and responding to queries and complaints from research participants or their representatives during the course of a research project;

6. 2. 6 Community Considerations

6.2.6.1 The impact and relevance of the research on the local community and on the concerned communities from which the research participants are drawn;

6.2.6.2 The steps taken to consult with the concerned communities during the course of designing the research;

6.2.6.3 The influence of the community on the consent of individuals;

6.2.6.4 proposed community consultation during the course of the research;

6.2.6.5 the extent to which the research contributes to capacity building, such as the enhancement of local healthcare, research, and the ability to respond to public health needs;

6.2.6.6 A description of the availability and affordability of any successful study product to the concerned communities following the research;

6.2.6.7 The manner in which the results of the research will be made available to the research participants and the concerned communities.

Appendix 7: List of Information that Should be Given to the Study Participants

Citation: *World Health Organization. Handbook for Good Clinical Research Practice (GCP): Guidance for Implementation. 2005 (page 62 – 64).*

List of Information that should be given to the study participants / participants in accordance with GCP

GCP recognizes that certain essential elements of informed consent should be included in the informed consent discussion, the written informed consent form, and any other information to be provided to participants who participate in the study. All information must be communicated in a comprehensive and understandable manner to the trial subject. This includes, but is not limited to:

- Title of the protocol.
- Identity of the sponsor.
- Identify of the clinical researcher and institutional affiliation of the researcher.
- Source of research funding (e.g., public, private, or both).
- That the trial involves research.
- That the subject's participation in the trial is voluntary and that the participant may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the participant is otherwise entitled.
- The purpose of the trial.
- The trial treatment(s) and the probability for random assignment to each treatment.
- The trial procedures to be followed, including all invasive procedures.
- The subject's responsibilities.
- Those aspects of the trial that are experimental.
- The reasonably foreseeable risks or inconveniences to the participant and, when applicable, to an embryo, fetus or nursing infant.

- The reasonably expected benefits. When there is no intended clinical benefit to the subject, the participant should be made aware of this.
- The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
- The compensation and/or treatment available to the participant in the event of trial-related injury.
- The anticipated prorated money or other forms of payment (e. g. , material goods), if any, to the participant for participating in the trial.
- The anticipated expenses, if any, to the participant for participating in the trial. This may include expenses to the participant for routine medical care for conditions that are not within the scope of the research.
- That the monitor(s), the auditor(s), the iec/irb, and the regulatory authority (-ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the participant or the subject's legally authorized representative is authorizing such access.
- That records identifying the participant will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
- The potential risks should confidentiality measures be compromised (e. g. , stigma, loss of reputation; potential loss of insurability).
- That the participant or the subject's legally authorized representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
- The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
- The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

- The expected duration of the subject's participation in the trial.
- The approximate number of participants involved in the trial.

"… Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the researcher. " (The Belmont Report)

Due consideration should be given to obtaining consent for the collection and/or use of biological specimens, including future purposes. Guidance is developing in this area (see CIOMS International Ethical Guidelines; CIOMS Report on Pharmacogenetics – Towards improving treatment with medicines, 2005; the Council of Europe Steering Committee on Bioethics (CDBI) Additional Protocols to Oviedo Convention, 2005).

Appendix 8: The Belmont Report

Citation: *Ethical Principles and Guidelines for the Protection of Human Subjects of Research, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research April 18, 1979*

AGENCY: Department of Health, Education, and Welfare

ACTION: Notice of Report for Public Comment.

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by creating the National Commission for the Protection of Human Participants of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human participant and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: **(i)** the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, **(ii)** the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, **(iii)** appropriate guidelines for the selection of human participants for participation in such research and **(iv)** the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four- day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy

reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, it available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U. S. Government Printing Office, Washington, D. C.

20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

Ethical Principles & Guidelines for Research Involving Human Participants

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human participants in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes intended to assure that research involving human participants would be carried out in an ethical manner.

The codes consist of rules, some general, others specific that guide the researchers or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human participants are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in

research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

Part A: Boundaries Between Practice & Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human participants or research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when "research" are not carefully defined.

For the most part, the term, "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. By contrast, the term "research" designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a format protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovations does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element or research in an activity should undergo review for the protection of human subjects.

Part B: Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficences and justice.

1. Respect for Persons. – Respect for person incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that participants enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as participants of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for person would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle or respect itself.

2. Beneficence. – Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well- being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. Two general rules have been formulated as complementary expression of beneficent actions in this sense: **(1)** do not harm and **(2)** maximize possible benefits and minimize possible harms. The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment. " Learning what will in fact benefit may require exposing persons to risk. The problem posed by

these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks. The obligations of beneficence affect both individual researchers and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, researchers and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures. The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children.

Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children – even when individual research participants are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application or previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research and presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice. – Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved. " An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all

commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are **(1)** to each person and equal share, **(2)** to each person according to individual need, **(3)** to each person according to individual effort, **(4)** to each person according to societal contribution, and **(5)** to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research participants fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research participants in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These participants were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research participants needs to be scrutinized in order to determine whether some classes (e. g. , welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and

that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

Part C: Applications

Applications of the general principles to the conduct or research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of participants of research.

1. Informed Consent. – Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied. While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that participants are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the participant the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how participants are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously

undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the participants should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing participants of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to participants that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that **(1)** incomplete disclosure is truly necessary to accomplish the goals of the research, **(2)** there are no undisclosed risks to participants that are more than minimal, and **(3)** there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the researcher .

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Researchers are responsible for ascertaining that the participant has comprehended the information. While there is always an obligation to ascertain that the information about risk to participants is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of

comprehension.

Special provision may need to be made when comprehension is severely limited – for example, by conditions of immaturity or mental disability. Each class of participants that one might consider as incompetent (e. g. , infants and young children, mentally disable patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these participants to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the participants from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the participant should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the participant from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the participant is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence – especially where possible sanctions are involved – urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence

would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitle.

2. Assessment of Risks and Benefits. – The assessment of risks and benefit requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the researcher, it is a means to examine whether the proposed research in properly designed. For a review committee, it is a method for determining whether the risks that will be presented to participants are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research participants are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of participants in society). Previous codes and Federal regulations have required that risks to participants be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research participant will normally carry special weight. On the other hand, interests other than those of the participant may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to participants and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, no arbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and researchers less participant to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether a researcher's estimates the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following

considerations; **(i)** Brutal or inhumane treatment of human participants is never morally justified. **(ii)** Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human participants at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. **(iii)** When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the participant – or, in some rare cases, to the manifest voluntariness of the participation). **(iv)** When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. **(v)** Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects. – Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of participants of research at two levels: the social and the individual. Individual justice in the selection of participants would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research.

Social justice requires that distinction be drawn between classes of participants that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of participants (e. g. , adults before children) and that some classes of potential participants (e. g. , the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual participants are selected fairly by researchers and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research participants fairly, and even if IRBs are taking care to assure that participants are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or researchers may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research participants if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such a racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

(1) Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U. S. Department of Health, Education, and Welfare Codes for the conduct of social and behavioral research have

also been adopted, the best known being that the American Psychological Association, published in 1973.

(2) Although practice usually involves interventions designed solely to enhance the well- being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e. g. , blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e. g. , vaccination, which protects both the person who is vaccinated and society generally).

The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general destination between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

(3) Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

Appendix 9: World Medical Association Declaration of Helsinki

Citation: *World Medical Association, 2000. Declaration of Helsinki, ethical principles for medical research involving human subjects. 52nd WMA General Assembly, Edinburgh, Scotland.*

(Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975,35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002 Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004)

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human participants includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient. "

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human participant should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human participants is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is participant to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be participant to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Researchers should be aware of the ethical, legal and regulatory requirements for research on human participants in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human participants set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human participants must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources

of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human participants should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the researcher , the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human participants should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human participant must always rest with a medically qualified person and never rest on the participant of the research, even though the participant has given consent.

16. Every medical research project involving human participants should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the participant or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human participants unless they are confident that the risks involved have been adequately assessed and can be

satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human participants should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human participants are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The participants must be volunteers and informed participants in the research project.

21. The right of research participants to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential participant must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The participant should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the participant has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the participant is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research participant who is legally incompetent, physically or mentally incapable of

giving consent or is a legally incompetent minor, the researcher must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a participant deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the researcher must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research participants with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the researchers are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists[1] (see part1 below).

30. 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[2] (see part2 below).

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods

[1] **Note of clarification on paragraph 29 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or - Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be participant to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

[2] **Note of clarification on paragraph 30 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Appendix 10: Ethics of Clinical Research: An Islamic Perspective

Citation: *Fadel HE. Ethics of clinical research: An Islamic perspective. Journal of the Islamic Medical Association of North America. 2010;42(2).*

Abstract

Medical progress depends on clinical research that at some point has to involve human subjects. The human rights of research participants must be protected. Ethical principles and guidelines have been developed by international organizations such as the World Medical Association (WMA) and the Council for International Organizations of Medical Sciences (CIOMS). The Islamic Organization for Medical sciences (IOMS) in Kuwait convened a meeting in Cairo, Egypt, in 2004 and produced a document advancing an Islamic viewpoint on these principles and guidelines. In this paper I discuss all these documents. The guidelines developed by CIOMS are in general agreement with Islamic principles i. e. respect for the person, bringing benefit, avoiding harm, and justice. However some differences exist to which I alluded. I also added some personal opinions. Muslim physicians and scientists should get involved in clinical as well as other medical research. It is farḍ kifāya (collective religious duty). They should be familiar with the ethical principles and guidelines and abide by them in their own research. Also, they should monitor externally sponsored research in their own countries to ensure that these guidelines are followed. Key words: Clinical research, ethics, Islam, Declaration of Helsinki, Council for International Organizations of Medical Sciences, Islamic Organization of Medical Sciences

Introduction

Academicians in faculty positions are traditionally involved in clinical research. Private practitioners can and should be involved in clinical research as well[1]. A requirement of clinical research is that it conforms to internationally recognized ethical guidelines. For Muslim physicians, conforming to Islamic ethical guidelines is an added requirement. In this article, I

will discuss the international guidelines and Islamic viewpoints regarding these guidelines. **Muslim Obligation to Conduct Research**.

Muslim countries are, in general, lagging behind in research, including medical research, despite their collective material and human potential. This is very ironic, noting that Muslim physicians of the past were the pioneers of scientific and medical research and were the first to employ scientific experimentation[2-5]. It is worthwhile to emphasize the importance laid by Islam on the pursuit of learning. There are several Qur'anic verses and traditions of the Prophet to this effect. The first revealed verses of the Q ur'an state: Recite in the name of your Lord, Who created. He created man from a leech-like structure. Recite, and your Lord is Most Generous, Who has taught by the pen. He taught Man that what he knew not[6]. Allah also says, addressing the Prophet, S ay, "My Lord, increase my knowledge[7]. "

Allah asks us to look inside ourselves and at the universe to dis cover God's laws. Let man consider from what he is created[8]. And in another verse: Will they not reflect on camels, how they are created; the sky, how it is raised; the mountains, how they are erected; and the earth, how it is leveled[9]. Learning in Islam is not limited to religious studies. Early Muslim scholars used to acquire an extensive knowledge, not only in jurisprudence (fiqh), Qur'an, and linguistic studies, but also in medicine, chemistry, and natural sciences. Knowledge has to be based on evidence. Allah says: Can there be another god besides Allah? Say bring forth your proof if you are telling the truth[10]!

Based on the above, scientific research is considered by some scholars as farḍ kifāya (collective religious duty). The Prophet Muhammad صلى الله عليه وسلم is reported to have said: Allah created disease and its cure except senility (death). Children of Adam, seek the cure but use not ḥarām (forbidden) things[11]. This hadith makes it incumbent on us to investigate the causes of disease and to try to find cures. This can only be achieved by undertaking both basic and clinical research.

International Ethical Guidelines for Clinical Research

Clinical research must rest in part on experimentation involving human subjects. Research involving human participants creates a lot of potential pitfalls that unfortunately led to tragedies in the last century. The most well-known of these are the experimentation by Nazis on the prisoners and in the United States in the Tuskegee study of untreated syphilis[12]. This study was conducted by the U. S. Public Health Service (USPHS). Over the period of 40 years (1932-72), 399 syphilitic African Americans were followed to study the natural course of the disease without treatment[13-6]. The study patients were never informed of the availability of Penicillin, which in the late 1940s was found to be an effective treatment for their disease. The Nuremberg Code was promulgated in 1947 as a direct consequence of the trial of Nazi physicians who conducted research on the prisoners of World War II without their consent. The United Nations general Assembly adopted the Universal Declaration of Human Rights in 1948 and the International Convention on Civil and Political Rights in 1966. Its article seven states in part: "In particular, no one shall be subjected without his free consent to medical or scientific experimentation."

In parallel with these efforts, medical professionals worked on formulating principles of ethical use of human participants in research. The first such document, the Declaration of Helsinki, was adopted by the World Medical Association (WMA) in 1964 in Helsinki, Finland. This was updated several times. The last was in Seoul, South Korea, in 2008 at the WMA 59th General Assembly meeting[17]. The central point of the declaration is that medical research should be participant to ethical standards that promote respect for all human beings and protect their health and rights.

The Declaration of Helsinki consists of 35 articles divided into three sections: the introduction,

"Principles for All Medical Research," and "Additional Principles for Medical Research Combined with Medical Care. " This document stresses that in the field of biomedical research, fundamental distinction should be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of

which is purely scientific and without direct diagnostic or therapeutic value to the person subjected to research. Medical research should be participant to ethical standards that promote respect for all human beings and protect their health and rights.

The Declaration of Helsinki also stresses that some research participants are vulnerable and need special protection. The research should be approved by especially appointed ethical review committees. Each potential research participant should be adequately informed of the aims, methods, sources of funding, and potential risks of the study. They should be informed about their right to abstain from participation or to withdraw from the study without any reprisal. For a research participant who is a minor or legally incompetent, the researcher must obtain informed consent from the legal guardian. These and other vulnerable groups should not be included in research unless it is necessary to promote the health of the particular group from which they are recruited.

In the United States, the U. S. National Commission for the Protection of Human Participants of Biomedical Research was created in 1974 and produced the Belmont Report in 1979, which distilled principles of ethics related to research[18]. It addresses boundaries between medical practice and research; basic ethical principles such as respect for persons, beneficence, and justice; and informed consent, assessment of risks and benefits, and selection of subjects.

Another international organization, The Council for International Organizations of Medical Sciences (CIOMS), was founded in 1949 under the auspices of the World Health Organization (WHO) and the United Nations Educational Scientific Cultural Organization (UNESCO). CIOMS in association with WHO undertook its work on the ethics of biomedical research in the 1970s. It produced guidelines to enable the effective application of the ethical principles set forth in the Declaration of Helsinki, particularly in developing countries. Their first report was published in 1982. Following that, there were major developments, such as the outbreak of the HIV/AIDS pandemic and proposals to undergo large scale experiments with vaccines and medications. There were also rapid advances in biotechnology and an increase in multinational field trials involving vulnerable populations in developing countries. These developments raised new ethical issues, and in 1996 CIOMS updated its report and published International Ethical

Guidelines for Biomedical Research involving Human Subjects, updating it in 2002. This consisted of a statement of general ethics, a preamble, and 21 guidelines[19].

The Islamic Viewpoint on CIOMS Guidelines

The Islamic Organization of Medical Sciences (IOMS), based in Kuwait, translated this document into Arabic. It was then reviewed by a scholar of Islamic jurisprudence. The document and the latter's comments were discussed by a group of Muslim scholars, physicians, including myself, and other individuals with interest in ethics and the law. The Islamic viewpoint on each of these guidelines was studied in depth by this group and discussed in a three day conference held in Cairo, Egypt, in December 2004. The results of these deliberations were published as the International Ethical Guidelines for Biomedical Research involving Human Subjects: An Islamic Perspective[20]. In this paper I will summarize the CIOMS guidelines, the IOMS document, and add my personal opinions.

The CIOMS guidelines as well as the principles of the Declaration of Helsinki are based on the generally accepted ethical principles of respect of person, beneficence, nonmaleficence, and justice[21]. These four principles are in agreement with Islamic rules. Allah _ says: We have honored Adam's children[22]. Respect of the person is a major aspect of human dignity. Respect of the person gives him the right to make his own choices and decisions. In the context of research, no one should be involved in a research project without his free and voluntary consent. The Islamic principle that applies here is "No one is entitled to dispose of the right of human being without his permission" [20]

A basic purpose of Islamic law is to "secure benefits for people and to protect them from harm. "[20] This is termed beneficence in our lexicon at present. Another Islamic law states that "every action that leads to harm or that prevents a benefit is forbidden[20]. This is what is now called "nonmaleficence. " In cases where benefit and harm are not absolute, which is the usual case in biomedical research, the rule that applies is that "if a less substantial instance of harm and an outweighing benefit are in conflict, the harm is forgiven for the sake of the benefit. "[20] Justice is an established principle in Islamic law. Allah _ says God enjoins justice and charity[23]. Justice

means equity and fairness, and charity is either the acquisition of benefit or the prevention of harm. Now, I will discuss these guidelines individually.

Document 1: Ethical Justification and Scientific

Validity of Biomedical Research involving Human Participants In agreement with this guideline, the performance of research on human participants is Islamically acceptable. However, it should be useful and responsive to the five purposes of Islamic law (*maqāṣid alsharī` a*), i. e. the safeguarding of one's religion, life (and health), intellect, progeny and property/ resources, and that it should not cause harm. On the other hand, a person who pursues scientific knowledge to cause harm is participant to God's wrath. God says: And they learn what causes them harm and brings them no benefit[25], and they already know that whoever purchases it has no share in the hereafter[24]. The Prophet صلى الله عليه وسلم asked God's refuge from learning that brings no benefit[25], the research should by no means lead to something prohibited. A researcher should comply with the framework of Islamic law in any research he undertakes. Moreover, a researcher should observe the rules and ethics of the profession, especially as they relate to the ethics of biomedical research. To be more specific, the research is Islamically acceptable under the following conditions:

1) The purpose of the study is to secure an absolute benefit i. e. , enhancing human health, or to prevent an instance of absolute harm that impairs health or to give priority to securing an outweighing benefit over preventing a less substantial instance of harm.

2) The benefit does not violate a legal stipulation nor contradict any absolute ruling of Islamic jurisprudence.

3) The research itself should be legitimate i. e. both the means and end must be legally permissible.

4) The design of study should be scientifically sound so that it should be more likely to achieve the purpose it is expected to accomplish. This is based on the rule that "every action that ceases to pursue its objective is unacceptable. "[20]

5) That the research team is qualified and competent to conduct the research as consistent with the Qur'anic guidance: God enjoins you to deliver your trusts to their rightful owners[26] and the Prophetic saying: Allah loves the person who is performing a job to do it in the best possible way[27].

Document 2: Ethical Review Committees

This document addresses the formation and role of the ethical review committees. A universally accepted standard is the establishment of ethical review committees to evaluate biomedical research and to ensure that its purpose and methodology are in accordance with the ethical guidelines. This concept is Islamically ordained. Medicine and biomedical research are so important that they need to be practiced under supervision. In that regard I like to point out that Muslims were the first to establish the practice of licensure to physicians and the system of *ḥisba* (inspection)[28]. This was meant to ensure that all people in trades, including physicians, were behaving justly.

The ethical review committees, usually called institutional review boards (IRBs), consist of scientists, physicians, lay people, and legal personnel. In an Islamic country, it is recommended that the ethical review committee gets the opinion of an Islamic jurisprudence (*fiqh*) committee to be certain that the proposed study is within the guidelines of Islam. An Islamic rule is "A responsible adult is not to embark on any undertaking before he finds out how it is regarded by God. "[20] The document that ethical review committees should be independent of the research teams and sponsors is in agreement with Islamic principles. The ethical review committee is in effect giving testimony. For such to be Islamically acceptable, it must be made by a neutral party. To satisfy the requirement of validity of testimony, any material or nonmaterial rewards for the committees should not be contingent upon the outcome of the review (testimony).

Document 3. Externally Sponsored Research

In case the research is externally sponsored, i. e. by an institution or an industrial or drug company from another country, the scientific and ethical review should be conducted objectively, independently, and honestly in the country of the sponsoring organization. This is to

guarantee that the standard ethical controls are applied. These should not be less stringent when applied in another, possibly less developed country than the controls normally applied in the country of the sponsoring organization, as all members of the human race should be treated equally. Equity for all people is a basic tenet of Islam. Allah _ says: O mankind reverence your Guardian Lord who created you from a single person[29].

In addition, another ethical review should be conducted in the host country to make sure that the proposed research meets the health needs and priorities of that country. One of the purposes of Islamic law is "To place everything in its right place [on the list of priorities]"[20]

Document 4. Individual Informed Consent

This document stipulates that the researcher must obtain a voluntary informed consent from each prospective study subject. This is in conformity with Islamic law that calls for respect of the independence of every individual, his right to make his personal choices and arrive at decisions suitable for him without any trace of coercion or deception, and his right to be protected from injury, misleading inducement, or exploitation by others. The consent should be given willingly after the subject, if fully competent, receives and understands the necessary information.

This is stipulated in *fiqh* rule: "No one is entitled to dispose of the rights of a human being without his permission" and "no right of a human being can be canceled without his consent. "[20] The information should be given in a written format in a language easily understood by the individual, and the consent should be documented.

Document 5. Essential Information for Prospective Participants

This document details the necessary information that should be given to the potential participants for the research. The informed consent should be given with full knowledge and correct understanding of the content of his consent on the part of the subject.

Document 6. Obligations of Sponsors/Researchers

This document details the duties of both the sponsors and researchers to give the participants accurate information and neither withhold any information that may negatively influence the potential research subjects' decision to consent nor deceive them in any way. They should not include any explicit or implicit threats in their discussions with the potential subjects. Islamic jurisprudence stipulations support this guideline. These stipulations are: "mutual agreement cannot be reached under conditions of ignorance" and "consent to an unknown thing and acquittal from an unknown thing are not valid. "

Document 7. Inducement to Participate

There is no objection from the Islamic point of view to compensate research participants for lost earnings, transport, and other expenses that might be incurred as a result of participating in the research. Actually, the rule of reparation and the principles of justice and fairness make it necessary to compensate the participants adequately for their expenses. Additional financial or in-kind payments made to induce participation in research may imply undue inducement. If it pressures the participant to give consent not based on conviction, then it is legally prohibited. However, if such payment does not influence the subject's decision making, and he gives his consent, with his free will, his consent in Islamic jurisprudence is valid. Nevertheless there should be – in my view – some restriction. The additional payments given to a poor person, or the provision or even the promise of medical care to a person who does not have access to that care in less developed countries or uninsured individuals in Western societies, could be a significant inducement that may cloud the ability of the person to make a true informed decision. The person may consent to participate and expose himself to certain risks he would avoid were he not in need of such incentives.

Document 8. Benefits and Risks of Study Participation

The researchers must ensure that potential benefits and risks are reasonably balanced, and the risks are minimized. The need to strike a balance between potential benefits and risks in research involving human subjects, with the prospective benefits being more likely and the need to minimize risks, is included in a basic principle of Islamic Law. It says "if a less substantial

instance of harm and an outweighing benefit are in conflict, the harm is forgiven for the sake of the benefit. " If a benefit and an instance of harm are in conflict, priority should be given to the weightier of the two[20].

It is acceptable from a religious perspective to use the expected, significant benefits to society as a justification of the risks interventions pose to an individual who has no possible direct diagnostic, therapeutic, or preventive benefit. This is based on a rule of jurisprudence, "Public interests take precedence over private ones. "[20] This is different from the Helsinki Declaration and the CIOMS guidelines that emphasize that individual benefit precedes social benefits. This point needs further study by Islamic scholars to determine to what extent public interest supersedes individual interest as it relates to human clinical research.

Document 10. Research in Populations and Communities with Limited Resources

Before undertaking research in a population or a community with limited resources, the sponsor and researcher must make every effort to ensure that the research is responsive to the health needs and priorities of the community in which the research will be conducted. Also, any knowledge generated or any intervention or product developed as a result of that research must be made reasonably available for the benefit of that population or community. This document is consistent with the Islamic principle of justice and charity[23].

Document 11. Choice of Controls in Clinical Trials

This document can also be endorsed from an Islamic point of view as it requires researchers to observe, in dealing with human subjects, the obligation of trust when choosing the method of intervention to protect their human rights fully and ensure their safety. God enjoins you to deliver your trust to their rightful owners[26]. Whether the use of a placebo arm in clinical trials is ethically acceptable has been vigorously debated[30]. Against objection by scientists, the 2000 version of the Helsinki Declaration specifically prohibits the use of placebos, except in limited situations. CIOMS recommends the use of equivalency trials or add-on studies. Equivalency trials compare an investigational intervention with an established effective treatment and produce scientifically reliable data. An add-on design may be employed when the investigational therapy

and a standard therapy have different mechanisms of action. The treatment to be tested and the placebo are each added to the standard treatment to determine if the investigational therapy leads to a better outcome or to fewer side effects. If the use of a placebo arm is essential for the clinical trial to produce useful information and there is no resulting harm to the participants in the control arm, it will be Islamically acceptable. The rationale for that is that "although a sort of deception is practiced, the consequences are safe. "[20] In my view, it may cause harm if the research participant in the control arm is deprived of a currently accepted treatment. I believe that the concerned ethics review committee has to carefully examine each specific case, evaluate the possibility of harm to the participants in the placebo arm and try to work with the researcher to find an alternative study design.

Document 12. Equitable Distribution of Burdens and Benefits in the Selection of Groups of Participants in Research

This document is again in harmony with Islamic law, which calls for justice in all affairs of life[23]. So it is unfair that participants in a study share in the burdens i. e. the potential side effects or other hardships but they do not share in the benefits when a successful intervention is achieved but is not made available to them.

Document 13. Research Involving Vulnerable Persons

These include persons with limited capacities or freedom to consent or decline to consent. They may be mentally incapacitated, elderly people who developed varying degrees of dementia, residents of nursing homes, people receiving welfare benefits, the unemployed, patients in emergency rooms, some ethnic or racial minorities groups, homeless persons, nomads, refugees, prisoners, and patients with incurable diseases. Junior or subordinate members of hierarchical groups, for example medical and nursing students, employees of pharmaceutical companies and members of the armed forces or police, are all considered vulnerable groups. Their agreement to volunteer may be influenced by the expectation of preferential treatment if they agree and retaliation if they refuse. Ethical justifications for the involvement of these vulnerable groups are:

1. The research could not be carried out equally well with less vulnerable persons.
2. The research will lead to improved treatment of health problems unique to the vulnerable class.
3. They are assured that they will have reasonable access to any product that comes out of the research
4. The risk is minimal.
5. The agreement to participate is supplanted by the permission of a legal guardian or other appropriate representative.

This CIOMS document is in conformity with Islamic law. These individuals need their rights and interests protected. They should not be forced, pressured, deceived, or subjected to exploitation of their psychological condition or financial difficulties in order to make them consent to be research subjects. Such coercion or exploitation involves injustice that is disapproved by Islamic law. In a divine tradition, Prophet Muhammad صلى الله عليه وسلم quotes his Lord _, as saying: My worshippers, I have forbidden injustice on my part and made it forbidden among you, so do not be unjust to one another[31].

Thus, a special justification of recruiting vulnerable individuals to serve as research participants is required in Islamic Law[20], and, as stipulated in the CIOMS guideline, strict measures to protect their personal rights and interests should be taken.

Document 14. Research Involving Children

The participation of children is essential in research on childhood diseases and treatments given to children, including medications and vaccines. However, the researcher must ensure that the research could not be carried out equally well in adults and that the knowledge to be acquired is relevant to the health needs of children. Further, a parent or guardian must give permission, and the assent of the child should be obtained to the extent of that child's capabilities and a child's refusal to participate or to continue in the research should be respected.

Under Islamic rulings, a child under the age of puberty is incompetent and his "consent" to participate in biomedical research is not valid. Moreover, in variance with this CIOMS guideline, Islamically, the permission of the guardian is not legitimate except

a) when there is an absolute or outweighing benefit or when the child's condition needs urgent participation,

b) when there is general need to conduct research relevant to children's diseases, drugs,or vaccines, and c) if the risks involved do not exceed what is associated with a normal medical or psychological examination of the child or when the increase in risk level is slight and approved by an ethical review committee. These special circumstances are considered "necessities that render permissible what is usually prohibited" in Islamic law.

In another variance from the CIOMS guideline, a child's objection to participate in the study is not taken in consideration. The authority to withdraw from a study is only given to the guardian. An exception would be if the child is perceptive i. e. is close to puberty and his perception skills have developed sufficiently even though he is still under guardianship.

Document 15. Women of Reproductive Age as Research Subjects

Researchers should not exclude women of reproductive age from biomedical research. If participation may be hazardous if a woman conceives, the researcher /sponsor should offer her pregnancy testing and provide her with access to effective contraception before the research. In agreement with this guideline, Islamic jurisprudence considers the exclusion of women of reproductive age from biomedical research as unjust because it deprives them from potential benefit. Their participation is conditional on voluntary informed consent, including information on the precautions taken to spare her and her fetus if she becomes pregnant from any hazards. In Islamic law, it is unacceptable for the permission of a husband to replace that of his wife. That would be an affront to her human rights. Although not a requirement, it is preferable for a married woman to obtain her husband's consent. No such point is included in the

CIOMS guidelines.

Document 16. Pregnant Women as Research Subjects

Research involving pregnant women is complicated by the fact that it may present potential benefits and risks to both the women and their fetuses. However, pregnant women should be presumed to be eligible for participation in biomedical research as long as they are adequately informed about the benefits and risks to themselves, their pregnancies, their fetuses, their subsequent pregnancies, and their fertility. The research should be relevant to the particular health needs of pregnant women in general. Researchers should include in their protocols a plan to monitor the outcome of the pregnancy with regard to both the health of the woman and the short- and long-term health of the newborn. Islamically, there is no objection to the participation of pregnant women in biomedical research because of the potential benefit of the research to them and to their fetuses. Ideally, before enrolling pregnant women in biomedical research, the researchers should rule out any harm to the fetus. However, that is almost impossible to achieve.

The safety of new medications cannot be assumed from animal experiments or from the study of the pharmacology of the medication used. There will always be some risk. Islamically, accepting the possibility of such harm would nevertheless be permissible if the mother or the fetus is likely to gain an absolute or outweighing benefit. When there are potential risks for the fetus, even when they are minor or outweighed, the researcher should also obtain the consent of the father. This is not a requirement of the CIOMS guidelines. It states ". . . it is desirable in research directed at the health of the fetus to obtain the father's opinion also, when possible. "[20] In some instances, clinical trials are meant for the treatment of the fetus and not the mother. In these cases there are more risks to the mother without any benefit to her. In my opinion the most obvious example is in utero (prenatal) fetal surgery to correct a fetal birth defect. In these cases, the maternal instinct may unduly influence her to agree to such trials. Ethically and Islamically, the researchers should make an extra effort to explain the trial, the potential benefit to the fetus, and the potential complications in the neonatal management, the short- and long-term prognosis for the fetus/neonate/child and especially the short- and long-term complications for the mother before she agrees to participate in the trial. Safeguards should be established to prevent undue inducement to pregnant women to participate in the research for the sole benefit of the fetus. In

these circumstances I recommend that the ethics review committee establishes a special counseling team independent of the researcher .

Document 17. Safeguarding Confidentiality

The subjects' research data should be held in strict confidentiality. However, the participants should be told the limits, legal or otherwise, to the researcher 's ability to absolutely safeguard confidentiality and the possible consequences of possible breeches of confidentiality. Safeguarding confidentiality is a basic tenet of Islamic law. This is the "trust" between an individual and the physician/researcher . Exceptions from the requirement of safeguarding confidentiality are made in cases where concealing the confidential information causes greater harm for the person involved than that caused by revealing it or when revealing it brings a benefit that outweighs the harm of concealing it. This is based on the rule of the permissibility of commission of the lesser of two injuries to prevent the greater injury. Also, there are cases where revealing confidential information is permitted because it brings a social benefit or prevents public harm[20].

Document 18. Right of Injured Participants to Treatment and Reparation

Research participants are entitled to free medical treatment when they incur any injury or any other harm as a result of their involvement in the research. They are also entitled to equitable compensation for any impairment, disability, or handicap that result from their participation. In the case of death, dependents are entitled to compensation. Their entitlement is based on the principle of justice, the fourth principle of ethics. The same is true from the Islamic point of view. This is based on the Islamic legal rule of reparation, which makes it an obligation for a person who causes any damage to another to make equitable compensation for the loss. When a participant dies as a result of his participation in research, his heirs are entitled to monetary compensation, which is the blood money stipulated in Islamic legislation for accidental homicide. The implicit agreement between research sponsor(s) and involved participants entails a religious responsibility on the part of the former party to make up for the damages suffered by a participant as a result of participation in the research. However, it was pointed out during the

deliberations in the Cairo conference that it is permissible for the researchers or sponsors to obtain in advance the subjects' informed consent to waive the researcher 's responsibility, including the research subjects' entitlement to compensation for disability and handicaps when they are not deliberately caused.

This is based on the fact that Islamically, a competent individual is entitled to waive voluntarily any of his rights, provided that he does that completely voluntarily without any pressure, inducement, or deception. While this is true, in my opinion, there is danger of it being abused as it will be impossible to prove that the waiver was given truly voluntarily. I would think that waiving of the right to reparation ought not to be permitted. In my view, allowing waivers will make the researcher less careful in avoiding harm to the research subject. Further, I believe there is a difference between harm resulting from accepted treatment versus that resulting from investigational treatment in the course of conducting a clinical trial. CIOMS Document 19 specifically prohibits such waivers.

Document 19. Strengthening Capacity for Ethical and Scientific Review and Biomedical Research

In externally sponsored research, sponsors and researchers have an ethical obligation to ensure that biomedical research projects for which they are responsible in the host countries contribute effectively to national or local capacity to design and conduct biomedical research and to provide scientific and ethical review and monitoring of such research.

Document 20. Ethical Obligations of External Sponsors to Provide Health Care Services

External sponsors are ethically obliged to ensure the availability of health care services that are essential to the safe conduct of the research and for the treatment of participants who suffer injury as a consequence of the research. External sponsors should also ensure the availability of services to make a beneficial intervention developed as a result of the research reasonably available to the population.

Guidelines 20 and 21 both fall under the Islamic principles of justice and charity and that of reparation previously discussed.

Summary of the Differences between the Islamic Viewpoint and CIOMS Guidelines

Few differences exist between the two documents. A major difference is the importance that Islam puts on "public interest. " It takes precedence over private interest in special cases. This contrasts with Document 8 as well as with the Declaration of Helsinki.

CIOMS Document 14 requires the consent of the guardian for a child to participate in research study. Under Islamic rulings this is also necessary, but the permission of the guardian is legitimate only under the strict conditions outlined above. Further, the CIOMS document stipulates that the assent of the child should be obtained if possible. Islamically, that is not required. At the same time, the child's objection to participation in the study is not to be accepted if the guardian believes that participation is beneficial. However, if the child's perceptive skills have developed sufficiently, the child's objection can be taken into consideration. On the other hand, the CIOMS document respects a child's objection to participate.

When recruiting a married woman for research, it is Islamically preferable to obtain the husband's consent. This is not included in CIOMS Document 16. When recruiting a pregnant woman for a research study if there is any potential risk to the fetus even when minimal or outweighed the husband's consent should be obtained according to Islamic rulings, but not according to CIOMS Document 17.

Islamic rulings allow revealing confidential information if it brings social benefit or prevents public harm. This is not mentioned explicitly in CIOMS Document 18 but is implied in certain situations. The concept of public versus private interest is again invoked here as in the discussion about Document 8. It needs further elaboration by Islamic scholars.

Another difference relates to Document 19. Whereas Islamic rulings will allow waiving of liability against the researcher (s) under certain conditions, the document prohibits such waivers. I expressed my stand against the waiver.

Integrity in Clinical Research

It has been stressed in Document 1 and in the Islamic prerequisites for research that the researchers should be qualified and competent to conduct the study by virtue of their education and experience. I believe it is important to add that they need to be honest. Although honesty is implied in competency, it is better and more practical to have it as a separate trait. Integrity or honesty can be manifested in two aspects. The first is for an researcher , upon noting unexpected side effects or harm to the study subjects, to discontinue the study and notify the concerned IRB or ethics review committee. An example of this has been reported[32]. The second aspect is to never falsify research data. Unfortunately, there have been instances of "competent" researchers falsifying data. Article 30 of The Declaration of Helsinki touches on the subject:

Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human participants and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations, and conflicts of interest should be declared in the publication.

Reports of research not in accordance with the principles of this Declaration should not be accepted for publication[17]. These points cannot be stressed enough. Islam stresses honesty and truthfulness. It abhors false testimony under which falsification of scientific data falls: O you believe! Be staunch in justice, witness for Allah even though it be against yourselves or your parents or your kindred[33] …

. . . So shun the filth of idols, and shun lying speech[34].

Conclusion

In this paper I presented the current ethical principles embodied in the Helsinki Declaration and the guidelines the CIOMS established for the application of these principles. They are mostly in conformity with Islamic law. I did point out some of the differences. Some of these are outlined

in the "International Ethical Guidelines for Biomedical Research (An Islamic Perspective). "[20] Other differences represent my personal viewpoints. It behooves Muslim researchers to fully abide by these principles and guidelines. Muslims who have *taqwā* (God consciousness) should be the first to promulgate those ideals as we are given the privilege by Allah _to care for His most honored creation, humans.

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