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RESPECTING THE AUTONOMY OF VULNERABLE POPULATION IN MORE THAN MINIMAL RISK CLINICAL TRIALS.

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The participation of human subjects in clinical trials is important for the purpose of measuring the efficacy of any health-related intervention on health outcomes.[1] Such health-related interventions may include investigation related to the improvement and development of medical devices, drugs and even the use of cells in humans(1).

Depending on the prospective risk or the discomfort involved with the health-related intervention, clinical trials may be categorized as; minimal risk, or more than minimal risk. In the context of clinical research, minimal risk is defined as the harm or discomfort expected to occur to an individual, that is not greater than the risks of those aspects, in the daily life or routine examinations.[2] In contrast, any clinical trial with greater than minimal risk is considered as a more than minimal risk clinical trial.[2] This category of risky clinical trials require the participant to use his or her discretion and freedom to make mature, uncoerced and informed decisions, with regard to his or her involvement in the clinical research process. However, there are certain individuals who lack either the capability, and/or possess limited decision making capacity to protect their own interest in trials involving more than minimal risk.[3] Besides limited decision making capacity or inability to consent, a person may be unable to protect himself or herself in research due to poor economic background, limited intellectual ability or the presence of specific disease which is desirable in the research process.[4] These types of people are termed as "vulnerable" in the research context and are predisposed to harm by researchers, either "intentionally" or "negligently".[5] Therefore, the concept of vulnerability in research setting calls into question, the participation of such subjects in more than minimal risk clinical trials, where the risk of injury is significantly higher than normal.

Many national and international research ethics guidelines have been formulated to protect vulnerable populations, however; they have not comprehensively discussed more than minimal risk clinical trials. Numerous studies have explored the unique exploitable position of vulnerable groups in clinical trials.[6-8] A particularly relevant study was published by Marcantonio et. al. which reported in depth, the challeges faced by members of vulnerable groups with regards to participation in clinical research process including more than minimal risk clinical trials.[8] These challenges may hinder the participation of vulnerable groups in more than minimal risk clinical trials, and thus restricting advancements of medical knowledge for the benefit of such groups.

This paper discusses strategies for the advancement and protection of the rights and interests of vulnerable groups for their ethical participation in trials involving more than minimal risk. The objective of this paper is to explore novel ideas that could supplement the existing research ethics guidelines for morally accepted participation of such groups in risky trials.

The Concept of Vulnerability

It is important to understand the concept of vulnerability as it is the key in designing the framework of ethical guidelines that protect the "susceptible" groups in more than minimal risk clinical trials. It is important to state here that the goal behind using this concept in formation of ethical framework of guidelines is to protect the vulnerable groups from harm or discomfort and not to exclude their participation by labeling them "vulnerable".

Vulnerability is a broad concept in the context of research.[3] Vulnerability may include limitations in providing/communicating informed consent, nevertheless, it is not restricted to that. However, published literature includes some studies that have described vulnerability only in the context of informed consent, ignoring the other facets of vulnerability.[9,10] Vulnerability encompasses numerous distinct aspects that may alone or inconjunction with limitations in providing informed consent render a person as susceptible to greater harm than an average participant.[3] A comprehensive overview of vulnerability, taking in to account all of the facets of this term, is therefore

necessary.

The Council for International Organizations of Medical Sciences (CIOMS, 2016) involving biomedical research on human subjects provides detailed information about vulnerability keeping these distinct factes in view.[11] According to CIOMS (2016) information, vulnerability includes people with diminished or limited decision making capability, educationally and socially disadvantaged, limited resources. In addition, CIOMS (2016) definition also takes into account situational factors that may cause vulnerability and are important in the context of more than minimal risk clinical trials.[3,11] These situational factors may include the content of the research protocol, the environment of the research, or unfair distribution of burdens and benefits in the research process.[3,12] The situational factors in more than minimal risk clinical trials may comprise of "therapeutic misconception" where the participant thinks that he or she is undergoing the standard course of treatment while in reality he is receiving experimental treatment.[13]

A comprehensive analysis of all the factors involved with vulnerability in biomedical research, has been conducted by Kipnis, who has strived to provide an organized and wholistic view of vulnerability.[5] Kipnis discusses six types of vulnerability in biomedical research that illuminates the distinct problems and barriers faced by vulnerable groups. The six types include "cognitive", "juridic", "deferential", "medical", "allocational" and "infrastructural" vulnerabilities.[5]

Cognitive vulnerability: It includes the capacity to "deliberate" about the study and to make a decision based on the deliberations about participation in the study.[5] Circumstances that would make a person exposed to this type of vulnerability include immaturity, dementia, mental retartdation. It also includes educational deficits and unfamiliarity with the language.[5]

Juridic Vulnerability: This type of vulnerability is present when the candidate is affected by the authority of someone else, who may have an independent interest in the participation of that research.[5] The examples include institutionalized persons subject to the authority of the custodians, students subordinated to their professors.[5] It is of special significance when those in authority are somehow benefitting from the research.

Deferential vulnerability: This type of vunerability is present when the research candidate is considerate about the norms of deference or regard, that may conceal an underlying reluctance towards participation.[5] For example, a research candidate in the presence of their colleagues and friends, may be exposed to this type of vulnerability.

Medical vulnerability: Medical vulnerability may be present when a research candidate has been chosen partly because of a serious health related condition for which there is no effective treatment available.[5] A seriously ill person suffering from a disease for which there is no satisfactory treatment options available, may participate in risky trials in the hope of recovery, even though those traials are not designed to give the experimental drug at the therapeutic dose.[13,14]

Allocational Vulnerability: Allocational vulnerability is found when the research candidate does not have vital social commodities, that would be provided only when the candidate takes part in research.[5] This may includes people with a poor economic background.

Infrastructural vulnerability: Infrastructural vulnerability is found when the "political", "organizational" , "economic" and "social" setting of the research field, is devoid of the resources needed to carry out the study.[5] This is possible when the researcher conducting more than minimal risk clinical trial presumes that resources required to carry out the research are available.[8]

Vulnerability and Principles of Biomedical Ethics

Although members of the vulnerable groups have limited or diminished autonomy, their participation is nonetheless desired to represent them adequately. Their freedom of choice and willingness to participate in the research process can be respected in the light of the principles used in biomedical ethics. Linking the principles of biomedical ethics to the issues faced by the vulnerable groups, in the research context, could help in forming a "principled ethical framework" for safe participation of vulnerable groups in trials involving more tham minimal risk.[15-17] This type of framework could help and guide the researchers, with regards to the particiaption of the vulnerable groups in such clinical trials.

The concept of vulnerability can be linked to the "The Four Principles Approach" described by Beauchamp and Childress; the principle of "respect for autonomy", the principle of "beneficence", the principle of "non-maleficence", and the principle of "justice".[18]

The principle of "Respect for Autonomy" supports the idea of "privacy", "voluntariness", "choosing freely" and "accepting the responsibility of one's own choices".[18] The principle of respect for autonomy relies substantially on informed consent. Informed consent is not merely signing the consent form to fulfill the legal and institutional obligations.[18] Rather informed consent comprises seven elements: "competence", "voluntriness", "disclosure", 'recommendation", "understanding", "decision" and "authorization".[18] The "competence" is a prime component and can help to determine the participation of vulnerable groups in more than minimal risk clinical trials. However, the presence, absence or degree of competency required to make a mature and well informed decision, is variable among the

subjects taking part in clinical research. For example, the level of competency in a child is different from that of a seriously ill patient, although both are members of vulnerable groups. Based on the level of competency, one may be unable to understand, may be unable to develop a power of reasoning and/or even unable to express his or her preferences. For instance, a child may not able to develop a power of reasoning but still has ability to express his or her wishes and/or preferences. Therefore, in such cases where a member of vulnerable group has limited cognitive ability to execute his power in making decision, the principle of "beneficence" can help them with their decision making process.

The principle of "beneficence" can help the individuals with limited decision making capability, in making legitimate and important decisions regarding their participation in research process.[18] Thus, it could enable researchers to assist research candidates, in determining their preferences for involvement in research. However, the argument used to assist the person has to be non-paternalistic, so that it does not override the preferences of the person.[18] For example, the investigator could help the minor person (14 to 18 yrs) in determining his decisions for participation in more than minimal risk clinical trials by showing videos or effectively communicating with him. However, it should be non-persuasive. The exclusion of minors solely in the light of their age, with out giving consideration to their autonomy and competence regarding informed consent would lead to underrepresentation in more than minimal risk clinical trials. It is quite possible that the participating minor may be competent.

Besides the participation of people with limited decision making capacity in clinical trials, there are also persons who may become incompetent during the trial process. In such cases "advanced directives" can help the researchers to deal with involvement of incompetent person, at later stages in the research process.[1] Beauchamp & Childress discuss two types of advanced directives: "living will", and "Durable Power of Attorney" (DPA)(18). The "living will" represents the substantive directives given in advance by the competent person for specific circumstances.[18] The "living will" helps the researchers to decide the future participation of the person, when he or she becomes unconscious or incompetent to provide decision. However, the advanced directives given by the person should be clear and detailed. Secondly, the durable power of attorney (DPA) also protects the incompetent person, in state of unconsciousness. In this process, the research candidate designates some other person who may act on his behalf in specific circumstances, and is known as surrogate decision maker.[18] The surrogate decision maker should have an adequate knowledge and information about the thought process of the non-autonomous person and shoud make a decision as the non-autonomous person would.[19,20] Surrogate decision making may also be considered, regarding the involvement of non-autonomus persons, such as newborns in research. For such types of non-autonomous individuals, surrogate decision making is considered without the presence of advance directives in research.[20] The surrogate decision maker could be a family member, health care professional, institutional ethics committee or the judicial system.[20] However, it is quite possible that a surrogate decision maker, who is a family member, may have some conflict of interest. In such case, the researcher should report to higher authorities or judiciary system to investigate the situation.

Another important principle, the principle of "justice" advocates the "fair", "appropriate" and "equal" treatment in the research process.[20] The principle of justice can be defined as a two sided coin. On one hand, it protects people from "undue burden" or harm in research. On the other hand, justice is seen as fair access to research. In the light of this point, the vulnerable groups should have equal access to participation in clinical trials involving more than minimal risk as the normal competent adult does. Even though, the vulnerable groups have distinct physical, social and psychological needs, their exclusion based on their unique needs alone, should not deprives them from participation in more than minimal risk clinical trials. A study reported by Marcantonio et. al mentions that vulnerable old aged people desire to participate in clinical research for the benefit of society.[8] They should be given such opportunity but at the same time, it is important to address problems related to allocational, deferential, and/or infrastructural vulnerability, which may cause "unfair distribution of benefits and burdens" in research process. Thus, there is a need to pay attention to such issues rather than focusing on their 'vulnerable' status, leading to their exclusion in clinical research.

The four principles are recognized as "prima-facie" principles and "they are always binding unless there is a conflict".[20] In the case of conflict between the two existing principles, such as the principle of "respect for autonomy" and the principle of "beneficence", researchers need to balance the principles based on the justification provided at that point in time. The conflict between two principles is balanced based on their weight or strength in the particular case.[21] The principle with high demand overrides another principle depending upon different situations. Precisely, both "principlism" and "casuistry" play a significant role in guiding research ethics involving vulnerable groups in more than minimal risk clinical trials. A closer look at the rules and regulations for vulnerable populations and the history of their creation will help us understand the applicability of these principles in the real world.

International and national research ethics guidelines concerning vulnerable populations

The establishment of research ethics guidelines arose in response to the historically recognized misconduct of researchers. In the early twentieth century, when vulnerability was universally exploited, there were no

standard guidelines or a legal consent process. Several horrific experiments were documented in the period before the development of standard guidelines for human research subjects. For forty years between 1932 and 1972, the U.S. Public Health Service (PHS) conducted an experiment on 400 black men in the early stages of syphilis. These men, for the most part, were illiterate sharecroppers from one of the poorest counties in the state of Alabama, and were never informed about the disease that they were suffering from or of its seriousness and complications.[22] The unethical, unprincipled and inhumane experiments conducted by Germany during World War II are another example of disrespect of the autonomy of research participants, and thus making them vulnerable to the research process. These experiments were conducted on the unwilling inmates of concentration camps and were uncovered post-WWII in the Nuremberg trials.[23]

The first code of ethics concerning research involving human subjects came into being with the conviction of physicians at Nuremberg.[23] This code of ethics thus came to be known as the Nuremberg code, which influenced many countries since 1964 in regard to ethics in research as there were no national laws and regulations framed for individual countries.[3] The Nuremberg code gave rise to a more explicit document, Declaration of Helsinki in 1970.[3] Presently, there are many international and national guidelines to protect the rights and interests of subjects in research. These guidelines have been revised according to the needs of the time.[3] In addition to Declaration of Helsinki, the international guidelines include the Guideline for Good Clinical practice (ICH-GCP) and The Council for International Organizations of Medical Sciences (CIOMS) guidelines.[24] The International Ethical Guidelines for Biomedical Research involving Human Subjects by CIOMS and WMA DOH (World medical Association, Declaration of Helsinki) guidelines are widely accepted documents for the ethical conduct of research in humans.[24] Many countries have also formed their own guidelines for the protection of research participants, known as national guidelines, such as, The Belmont Report, in the United States. These guidelines do cover the principles for safeguarding the interest of vulnerable groups, however, they lack comprehensive steps about the participation of vulnerable groups in more than minimal risk clinical trial. Vulnerable groups may still suffer exploitation in more than minimal risk clinical trials due to the lack of information for such trials in the present guidelines.

In this paper, I take a detailed look at the guidelines to assess their weaknesses and strengths about protection of rights of vulnerable groups regarding participation in more than minimal risk clinicnal trials. Moreover, based on those features, I recommend addition of certain steps to make the guidelines more comprehensive and explicit about the participation of vulnerable groups in more than minimal risk clinical trials. I expect that this would give, these groups a better chance of participation and representation in more than minimal risk clinical trials without compromising their autonomy and interest.

WMA DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

The WMA Declaration of Helsinki, is currently accepted as the key document for research ethics around the world. It has undergone seven revisions and celebrated its 50th anniversary in 2013.[25] The major changes related to vulnerable populations were included in the 2000 revision.[26] Moreover, to deal with ethical issues in the conduct of clinical trials, the seventh revision, that occurred in 2013, also included funders, researchers and research participants.[25] Nevertheless, it still presents certain barriers in the participation of vulnerable subjects in more than minimal risk clinical trials.

i) In the preamble to the current revision, Declaration of Helsinki states that it is primarily "addressed to physicians".[27] Through this statement, it appears that the major responsibility for the conduct of trials lies with physicians or doctors. However, the clinical research process involves many people such as sponsors, researchers or other healthcare professionals.[25] Therefore, it should be addressed to all the persons who need to follow the guidelines presented in the document.

ii) The vulnerable groups have been mentioned in an individual section under paragraphs 19 and 20 in the latest version (2013).[27] The definition of vulnerable groups conveyed through these paragraphs is not specific and clear, which may confuse the researcher, while providing "special considerations" for such groups.[27] This type of challenge faced by the researchers may exclude the participation of vulnerable groups in trials involving more than minimal risk.

iii) The latest version of Declaration of Helsinki has stressed the topic of informed consent in the research process, however the information provided is confusing. It mentions in paragraph 25 "person incapable of giving consent" and "persons deemed incapable of giving informed consent" in paragraph 26.[27] While recruiting minors or teenage children in clinical research, it is unclear whether they should be followed according to paragraph 25 or paragraph 26. It also mentioned that a legally authorized person can consent for the "person incapable of giving consent".[27] However, Declaration of Helsinki's definition of incapable person is not clear. It does not clearly state the level of competence which is required to make decisions in the research process. Different types of research require different competence levels, depending upon the protocol.[28] More than minimal risk trials, such as drug trials, commonly require a higher competence level to understand and participate in the research process. To ensure the ethical inclusion of these participants in clinical research prcess, Declaration of Helsinki should

clearly state the difference between a competent and an incompetent person in research settings. In addition, Declaration of Helsinki should recommend the use of cognitive test while recruiting participants in risky trials to assess their level of competency in decision making process.[18]

(iv) Regular scrutiny for the trials involving more than minimal risk would ensure fair distribution of "benefits" and "burdens" in the research process.[16] The paragraph 23 in the latest version of Declaration of Helsinki's mentions that regular monitoring is required for ongoing studies.[27] Regular monitoring is an important requirement, as the current choice of participants may be different from their future choices. If the patient may choose to opt out of the research process in the future, it ensures the autonomy of the person in the entire research process.[29] However, paragraph 23 does not specify the intensity and frequency of monitoring required in more than minimal risk clinical trials.

v) Regarding the risks and burdens in the research process, Declaration of Helsinki mentions that when the risk outweighs the benefit, the physician should decide whether to modify, continue or stop the research procedure.[27] Therefore, the sole responsibility of controlling the clinical trials is in the hands of physicians. This could lead to various conflicts of interests in the trials involving more than minimal risk, such as, the physician may not terminate the clinical trial in order to accrue financial gains. Thus, to prevent this situation, other healthcare people such as, family physician of the research candidate or the member of the Research Ethics Boards should also be involved.

International Ethical Guidelines for Health-related Research Involving Humans Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO)

The Council for International Organization for Medical Sciences was founded in 1949 in collaboration with the World Health Organization and UNESCO (United Nations Educational Scientific and Cultural Organization).[11] It started its work related to ethics in biomedical research in the late 1970s. The issue of vulnerable populations came into notice in the second version of the CIOMS guidelines in 1993.[11] In 2016, the fourth version of the CIOMS guidelines came into being with more in-depth analysis of ethical issues involving translational research, participation of vulnerable groups in experiments and research in low resource settings.[11] Unlike Declaration of Helsinki, it mentions the rules for each group of vulnerable populations in a more organized manner. Regarding vulnerable groups, the 2016 version of the CIOMS guidelines provides a detailed description in the number 15th, 16th, 17th, 18th and 19th guideline.[11] It is worth noting that the CIOMS guidelines provided rules for different members of vulnerable groups (children, pregnant women and adults incapable of giving consent) under different headings, which makes it more clear and specific. Still, there is a need to make certain improvements in the guidelines to ensure safe inclusion of vulnerable groups in more than minimal risk clinical trials.

Guideline 16: Guideline 16 describes the protection of the interests of the adults who are incapable of giving consent.[11] The competence level for providing consent in CIOMS guidelines is explained in a better way as compared to Declaration of Helsinki guidelines. Guideline 16 mentions that the assent of the person needs to be held according to the capacity of a partially incapable person, and his refusal must be honored.[11] It has also provided the provision of consent from a lawfully authorized person for a totally incapable person. According to the guideline 16, the person incapable of giving consent should be allowed to participate in the "health related research" unless there is a "solid scientific explanation" for his exclusion.[11] However, this guideline did not make a distinction between various types of "health- related research". The word "health related research" is not limited to clinical trials. It also signifies the qualitative, observational and quantitative research studies.

Guideline 17: The guideline 17 talks about protecting the rights of children and adolescents. The guideline provides general rules for all the children and teenagers, however the physical and psychological needs of the 7 year old are quite different from the 15 year old individual. Due to the specific needs of each age group, the protocol design for different age groups may vary.[28] Thus, to increase the participation of children in more than minimal risk clinical trials and make the rules easier for researchers to understand, the guideline 17 should specify the rules/consdierations for different age groups. Secondly, guideline 17 states that the assent of the minor to take part in the health related research is necessary after obtaining permission from parents or legally empowered individuals.[11] Although the consent of parent or legal custodian is regarded as important, they should never be paid monetary compensation for participation of their child in research.[28] The guideline did not mention this point; however, it is important as it could lead to harm or discomfort in children.

Guideline 18: This guideline protects the rights of women in health related research.[11] Similar to Declaration of Helsinki, the CIOMS guidelines also mentions the need of "special considerations" for some groups. Women's autonomy is disrespected in some developing countries which prevents them from protecting their interest in research.[5] In one of the studies, it has been reported that the clinician researchers avoid the involvement of potentially pregnant women in the fear of legal consequences.[30] According to guideline 18, women must participate in the health related research with their own consent, rather than the consent of third parties.[11] Adult females must not be shut out of the

research process based on biological, societal or ethnic reasons and the researcher must pay attention to the psychological and physical needs of the women.[6,11] In addition, the guideline mentions that childbearing women need to be informed if the research carries any risk to her future pregnancy.

Guideline 19: Guideline 19 asserts that researchers must pay attention to the needs of lactating women. Special attention to the health and psychological needs of lactating and pregnant women must be paid in the "health related research".[11] Consent for the participation of the pregnant woman must be given by herself, and, if she wishes, she may consult the father of the fetus. The guidelines also mention that there is a the need to pay attention to the availability of resources required in the research process.

For all the members of the vulnerable groups (women, children and adolescents, lactating women, person incapable of giving consent), CIOMS guidelines mentions that such groups must participate in the research which involves minimal risk. If the risk anticipated is more than minimal, the research should be of "direct benefit" to the members of vulnerable groups. This type of statement could lead to automatic and inappropriate exclusion of such groups in more than minimal risk clinical trials. For instance, there are 4 phases of drug trials and the first 2 phases does not directly benefit the person. But, in order to reach phase 3 and phase 4 of the drug trial, the research must pass first 2 phases.[31] Therefore, I recommend that their willingness to participate should be encouraged, for all types of clinical trials by providing special protections and strict minnitoring at each stage of the research process.

Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS-2, 2014)

The Tri Council Policy Statement for the ethical conduct of research in Humans was adopted in 1998 by the government of Canada. The second version, TCPS-2, is an updated version of the 1998 version and was adopted in 2010.[1] The TCPS-2 document underwent some changes in December, 2014 and is followed currently for ethics concerning participation of human subjecs in Canada.[1] It represents the joint policy of three federal research agencies- Canadian Institutes of Health Research (CIHR), National Sciences and Engineering Research Council of Canada (NSERC) and Social Sciences and Humanities Research Council of Canada (SSHRC).[1]

Regarding acquistaion of informed consent for research from human subjects, TCPS-2 guidelines provide detailed information. It clearly mentions the participation of the intermediate person when language is a barrier to understanding the consent form.[1] This is particularly important for protecting the interests of the socially and culturally unassimilated participants in research setting. It also mentions the consent form should be in "plain language" to avoid misinterpretation and ease understanding for the research participants.[13,32] Further, to increase the participation of subjects who cannot sign the consent form, the guideline describes other appropriate methods of getting informed consent; such as oral or verbal consent.[1] This could provide an opportunity to illiterate people to participate in more than minimal risk trials.

Latest version of TCPS-2 states that the consent to participate in research process should be based on the decision-making capacity of the person and not their chronological age. Based on this change, the articles 3.9, 3.10 and 3.11 state that the person who is unable or legally incapable of giving consent should be involved with the decision to the maximum of his capacity.[1] In addition, article 3.11 preserves the autonomy of the individuals who had expressed their preferences in the research directives, however lost their decision making capacity during the research.[1] In this case, the preferences expressed in the research directives could help guide the researchers and authorized third parties.

Regarding the recruitment of women, children, elder people and persons with limited decision making capability, article 4.3,4.4,4.5 and 4.6 mentions that the Research Ethics Boards (REBs) must ensure that the trial involving more than minimal risk is being carried out to benefit the individual.[1] Similar to CIOMS guidelines, it mentions that the research should be of minimal risk if it does not directly benefit the person, who has limited decision making capacity. However, this could limit the participation of persons with limited decision making ability in some research, thus affecting their autonomy. It also stands against the point mentioned in article 4.7, which disregards the automatic expulsion of vulnerable groups from research based on the category to which they belong.[1] I suggest that the Research Ethics Boards should pay attention to the willingness of the vulnerable groups. There are some members of the vulnerable groups, such as minors and older population who can express their wishes or willingness to participate in such trials. Their willingness to help society by participating in indirect benefit research should be respected.[8] At the same time to ensure their morally accepted participation, it should be made sure that the willingness of such participants is not influenced by external forces such as the pressure of a family member or any financial gain in the research process.

For the welfare of research participants in clinical trials, chapter 11 in TCPS-2 guidelines, details some important terms such as "clinical equipoise", "duty of care" and "therapeutic misconception".[1] Clinical equipoise is considered important in the design and review of clinical trials and ensures that randomly assigned groups are at an equal probability of harm and benefits incurred in the trial procedure.[1] It observes the rule of "justice" in the participating subjects and therefore, prevents them from being 'vulnerable' in clinical trials. Further, to honor the

autonomy of participating subjects and to preclude them from being 'vulnerable', article 11.6 states that researchers must pay specific attention to the phenomenon of "therapeutic misconception".[1] To avoid "therapeutic misconception", the researcher or clinician must recognize the difference between the goals of research and the goals of standard clinical care in the consent process.[1] A study reported that "therapeutic misconception" may cause harm or discomfort to a seriously ill patient as they overlook the risk involved with clinical trial procedure in the hope of treatment.[13] Under "duty of care", it is the obligation of the physician or researcher to explain the benefits and burdens involved in the trial process involving therapeutic goals.[1] In addition to therapeutic research, clinical research also comprises trials with non-therapeutic goals. For instance, Phase 1 or Phase 2 drug trials are not mainly concerned with treatment.[31] Therefore, other health care professionals, who are not clinicians, such as pharmacists or biotechnologists, should also be made part of clinical trial process to avoid inappropriate enrollment of subjects in more than minimal risk clinical trials.

Monitoring for the safety and well being of participants is mentioned under article 11.7, however the intensity and frequency of monitoring required, depending upon the type of clinical trial has not been discussed. As clinical trials also require international sponsors, the guidelines have paid particular care to the financial conflict of interest and clinical trial budget in articles 11.10 and 11.11.[1]

There is no doubt that national and international guidelines have been set down to ensure the safe participation of vulnerable groups in research process and that various revisions have also been made to improve these guidelines.[25] However, there is limited information pertaining to more than minimal risk clinical trials involving vulnerable groups in the present guidelines. This limited information in the guidelines may act as a barrier for participation of vulnerable groups in more than minimal risk clinical trials and thus, disrespect their autonomy by not giving them the opportunity to participate. The lack of data in the medical research due to the exclusion of so- called vulnerable groups from clinical trials, including new drug interventions and investigations, could deprive them of valuable and efficacious future care. Thus, it is significant for the guidelines to comprehensively address the inclusion of such groups in more than minimal risk trials.

The CIOMS guidelines have expressed the need for participation of pregnant & breastfeeding women, children and adults with limited consent capacity in clinical trials.[11] However, CIOMS does not provide specific guidelines for more tham minimal risk clinical trials as it did not distinguish clinical trials based on the risk level. Similarly, the guidelines by Declaration of Helsinki mentions about clinical trials in general, not specifically about risky trials.[27] The guidelines should carefully scrutinize the barriers that lead to inappropriate exclusion of vulnerable groups in clinical research. Further, there is a need to specify the rules for each group of vulnerable populations participating in trials involving more than minimal risk using principled ethical framework. This is important because risk level in a particular clinical trial may vary depending on age or physical/mental disability. The research involving "minimal risk" for adults could prove "more than minimal risk" in the case of children.[6,28] Keeping this point in mind, rules for participation in more than minimal risk clinical trials should be clearly specified for all the members of vulnerable population. The usage of confusing terms in the guidelines could even prevent researchers from recruiting vulnerable groups in more than minimal risk clinical trials. The CIOMS guidelines use the word "health related research" for all the health linked research.[11] It lumps together various types of health linked researche such as observational researches, clinical tests, health related surveys, etc. The terms such as "clinical trials", "minimal risk" and "more than minimal risk' should be clearly stated in the document.

In the present era, when science and technology are progressing daily and biomedical research has revolutionized the study of medicine, clinical trials involving bodily interventions have become imperative.[31] Pharmaceutical drug trials are the most common clinical trials and can be included in "more than minimal risk" category.[31] The drug trial is a very vast research subject area and includes four phases: Phase I, Phase II, Phase III and Phase IV. These four phases are entirely different from each other and in the risk level.[31] The "Special needs" of the vulnerable groups may vary according to the amount of harm in each phase of the trial process and should be mentioned in the present guidelines. In addition, there is always a need for regular surveillance in such trials, especially for recruiting vulnerable groups. The regular monitoring has been stated in the present guidelines, however the intensity and frequency required for monitoring such trials is missing. The regular intense monitoring is required in trials involving more than minimal risk and should be stated in the guidelines according to the prospective risk or harm involved in trial procedure.

Last, but not the least, the clinical trial sponsors should also be involved during the formation of guidelines. The sponsor can be an individual, company, foundation or establishment which assumes responsibility for the installation, management and funding of a clinical trial. Their involvement could increase the participation of incapacitated individuals in the trials involving more than minimal risk. As reported in one of the studies, the latest version of the Declaration of Helsinki, included sponsors, funders or research participants for forming the guidelines, but their involvement seems to be brief and all the aspects related to clinical trials have not been discussed.[25] I suggest the active participation of such

stakeholders in the future revision of Declaration of Helsinki and other guidelines. Their active participation is necessary as the companies sponsoring the research, are responsible for resource allocation in clinical trial procedure. There are some groups such as children or elder people who are unable to access the research sites due to limited availability of resources. Marcantonia et. al reported the barriers that prevents the vulnerable elder population to participate in the clinical trials.[8] The study reported that the members, who are willing to participate in the trials, are limited due to the barriers such as travel, duration of interviews or unavailability of written results conducted during the trial.[8] Therefore, the above mentioned barriers can, indirectly, affect the autonomy of the member of vulnerable groups in more than minimal risk clinical trials. Such population, which is willing to participate to benefit the society, ought to be given the chance. Their autonomy can be respected by providing them the resources, needed to participate in such trials. This may include the modifications in allocation of resources in the study design according to the type of population involved. The modifications in the study design such as conducting home interviews or flexible appointment times could help solve this problem in older vulnerable people.[8] Conducting home interviews for the older population and children, short and flexible appointment times for seriously ill patients or incentives such as free parking for the economically disadvantaged population are some of the possible measures that could be taken into account while recruiting vulnerable population in clinical trials. Determining the scope of clinical trials in terms of funding and resource allocation includes multiple stakeholders. Thus, the combined endeavor of researchers and international sponsors in further revisions of national and international guidelines could help in respecting the autonomy of vulnerable groups in more than minimal risk clinical trials.

CONCLUSION

The participation of vulnerable population in a clinical trial is important. There is no denying the fact that the risk taken with more than minimal risk clinical trials is significant and involve the people with special needs more than the normal masses. However, their exclusion based on this point cannot be rationalized and, is indirectly a way of disrespecting their autonomous state or willingness to participate in the clinical research process. The guidelines need to be revised for addition of a new section, or a chapter regarding participation in more than minimal risk clinical trials. The detailed description about the people with special needs in accordance with high, moderate and minor increases of risk due to involvement in trial over minimal risk, would help in providing them with the opportunity to participate in such trials.

The appropriate description of the concept of vulnerability being conveyed through guidelines would remove the stigma associated with recruiting vulnerable groups in research. Further, involvement of the people who deal specifically with more than minimal risk clinical trials, such as international sponsors, researchers and clinical investigators, would help in naming the problems and barriers faced by vulnerable population in such trials.

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