

ETHICS OF TRIALS IN HEALTHY VOLUNTEERS

*Article Review by Orgah Adikwu Emmanuel, Nigeria
(M.Sc., Ph.D., in Clinical Research Student of Texila American University)
Email: - emmaorgah@yahoo.com*

INTRODUCTION

Ethics of clinical research have raised many issues of debate. This, according to Friedman et al., (2010) range from the expected professional obligations of physician, whether clinical research is a worthy cause especially when clinical equipoise is in doubt and what research may imply for patients and societal good. Other such related issues of debate include: which should be an appropriate study design, who should serve as the control group, should placebo be allowed, how well informed is informed consent, equitable conduct of trials among disadvantaged/underprivileged societies, the poor, avoidance of exploitation, how conflict of interest could mar research objectives, protection of subjects confidentiality, right of access to data, control of specimens, and publication ethics.

These general issues of ethical debate are largely based on studies involving subjects who are ill and less on those concerning healthy volunteers. This is perhaps because the concept of medical research ethics is focused on safeguarding the physician-patient relationship which inadvertently comes into question when seeking scientific knowledge for health improvement, (Miller and Rosenstein, 2003). It may be perceived also that the history of ethics emanated from the reckless behaviour of some physicians while dealing with their patients. It is therefore perceived that research involving healthy volunteers is less likely to evoke ethical concern since they are not ill, are not imposed with a condition capable of compromising their autonomy and decision-making capacity, and there is no reason for morbidity in their ability to give informed consent. Yet, research involving volunteers have features that can diminish prospective participants' ability to exercise free and informed choice and the level of uncertainty characterizing this form of inquiry makes subjects vulnerable to harm.

It is expected that healthy volunteers do not experience "therapeutic misconception" hence should not be confused about the differences between being a research subject and being treated for a health condition, (Appelbaum et al., 1987). They are expectedly not under the control of the study physician hence should not feel pressure to participate in research. This notwithstanding, healthy volunteers possess characteristics that could make them subjects of ethical abuse even though perceived as non-vulnerable. The area of ethical concerns arises mostly from the monetary payment to volunteers for inconvenience and lost time (undue Inducement), risk assessment and inappropriate informed consent procedure.

THE NECESSITY FOR VOLUNTEERS

It may be necessary to ask, ‘why use healthy volunteers since there may be no perceived benefits for participation on their part’? The moral suasion for clinical research is that it provides the needed scientific knowledge to improve Medicare for the benefit of society. Research volunteers are the people who come forward to aid society by exposing themselves to the risk of research. Therefore their role as research subject is of particular ethical interest because they provide the necessary relief to society and support the moral context of clinical research in being exposed to risks of harm for the potential benefit of future patients and society, (Miller, 2003).

From a medical perspective, healthy volunteers have no chance to benefit from research participation. The risks to which they are exposed can be justified only by the value of the knowledge to be gained from their research participation. A variety of clinical studies with healthy volunteers pose more than minimal risks of harm or discomfort.

UNDUE INDUCEMENT

Phase I trials for instance enrol healthy volunteers and provide payment as reimbursement for expenses. Such payments are based on lost time, degree of pain and risk involved from the study procedures. When the amount paid is such that the volunteer subject, due to economic gain, makes unwise or dangerous decisions, it is seen as excessive and “coercive” or amount to an “undue inducement”, (Dickert and Grady, 1999).

In a study by Bentley, and Thacker, (2004), it was clearly observed that payments could unduly induce subjects into taking part in a study that they would otherwise not participate in. It was also observed that inducements causes subjects to conceal information that would disqualify them from the study since it will mean loss of such source of income. This study suggests that monetary payment increases respondents’ willingness to participate in research regardless of the level of risk and higher levels of payment make respondents more willing to participate, even if the study is relatively risky. Although the practice of paying subjects to participate in research is not new, it is a critical ethical criterion that tends to invalidate the informed consent process and the research outcome.

CIOMS guideline 7 on the subject of inducement distinguishes between acceptable and unacceptable forms of remuneration for participation in research. It states in part: “*Subjects may be reimbursed for lost earnings, travel costs and other expenses incurred in taking part in a study. Subjects, particularly those who receive no direct benefit from the research, may also be paid or otherwise compensated for inconvenience and time spent. The payments should not be so large, however, or the medical services so extensive as to induce prospective subjects to participate in the research against their better judgment ...*”

It is pertinent therefore that volunteers should never be paid more for taking on more risk and investigators should carefully review the regulatory guideline on appropriate remuneration for

research participation without jeopardising volunteer autonomy and capacity for right choice. Ethics review committees often have guidelines as to appropriate amounts for various kinds of studies and procedures and must ensure that the amount provided does not create an undue influence. To ensure that this ethical criterion is not violated, the investigator should carefully review financial inducement with the ethics committee and determine the appropriate amount for the study.

RISK ASSESSMENT

Aside from the ethical premise of financial coercions and undue inducement as the core issues that befuddle the capacity for right choice of the healthy volunteer, the other central ethical issues surround the inappropriate risk benefit assessment. The code of ethics for clinical research as envisioned in the Declaration of Helsinki, states that “Medical research involving human subjects 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 subjects are healthy volunteers”, (JAMA, 2000).

It is expected that research involving volunteers should be of minimal risk or at least all adverse effects should be known and expected with very clear knowledge of how to manage them. Or according to The Declaration of Helsinki: “every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others” (WMA, 2 principle I.5). This situation was tested in 2001 when a healthy research subject in a study aimed at understanding the pathophysiologic characteristics of asthma died, (Steinbrook, 2002). This raised a heightened ethical concern about the risks of research with healthy volunteers and the need to ensure adequate subject protection, (Steinbrook, 2002). Since then, there has been such other incidence as the severe neutropenia among healthy clinical trial participants exposed to standard doses of rifabutin, the Jolee Mohr (Gilbert, 2008) and Jesse Gelsinger cases, (Steinbrook,2008), as well as subjects in the 2006 study of the investigational agent TGN1412, (Suntharalingam, *et al.*, 2006). These incidences show the dangers that can arise in healthy volunteer research and underscores the importance of scrupulous design and conduct of clinical investigation to protect research subjects. (Apseloff, 2003; Flexner and Barditch-Crovo, 2003)

Therefore, researchers have the responsibility to satisfy this particular ethical requirement by ensuring that a proposed research study has a favourable risk-benefit ratio. To achieve this, researchers must engage in a sequence of steps to identify, minimize and judge that the risks posed by the trial and its research interventions, is justified by the potential benefits of the study, first to the volunteer (if any) and to society.

The process of risk identification involves the following three domains of assessment:

- What is the **probability** that the study pose a risk and what have been put in place to minimise such probable risk?

- What is the **magnitude** of anticipated risk and is it justifiable or is it avoidable?
- What is the **duration** of harm, if justifiable how and what management protocols have been put in place.

The responsibility of the researchers is thus to ask the following three questions and seek all the means in assessing and addressing the risks posed by the trial.

- ✓ What is the chance that interventions of the research protocol will produce various harms to the health or well-being of volunteer? What can be done to mitigate this?
- ✓ How serious is the potential harm from interventions of the study? From risk benefit ratio is it justifiable?
- ✓ How long is the potential harm expected to last if it occurs?

In complying with the declaration of Helsinki, a researcher must be thorough while conducting this risk benefit assessment by considering all forms of risks including temporary discomfort or distress associated with research interventions, as well as lasting physical harm. The researcher should assess and determine that the risks have been minimized within the context of a rigorous scientific design and conduct of a valuable and rigorous clinical research. This implies that risk minimization is subjective and requires at all time a comparative evaluation in strict adherence to guideline and regulations with reference to the objective of the study.

Carrying out this risk assessment imply also that a researcher must evaluate the proposed research protocol in comparison with other alternative ways that could provide answers to the research question while demonstrating scientific rigour and posing minimal risk to the volunteer. If the evaluation and assessment by the researcher reveals such alternative, the moral duty of the researcher is to adopt this alternative or at the minimum eliminate the procedure in the protocol that constitute the higher risk without jeopardising the scientific rigour of the trial. Procedures of higher risks of physical harm or serious discomfort may not necessarily produce a more valuable data.

Another way of mitigating research risk in volunteers is to critically evaluate the volunteers themselves. This constitutes conducting a multi-dimensional assessment of the research protocol by evaluating the method and the subjects of research. Subject evaluation falls under the category of critical review of the exclusion criteria. A strictly defined exclusion criterion will eliminate candidates with probable heightened risk from the study design and interventions.

Astuteness on the side of researchers may go a long way in minimising risk as published research findings on procedures and investigational products could guide the investigator opportunities to measure risk. Thus, a thorough review of the literature is essential before and during the study to proactively identify probable risk factors and manage them. Such data will reveal whether

investigational products or procedures have been associated with serious adverse events and perhaps suggest ways to minimize such risks based on experience.

Research, like day to day living, comes with natural risks but like the first aid kit kept in homes, the researcher should be well prepared ahead of time by establishing good clinical practices, establishing quality control measures and trial monitoring procedures to monitor the condition of the volunteers serving as research subjects and if need be, intervene early to counteract adverse events. In severe cases, it is the moral responsibility of the investigator not only to report but be prepared remove the subject from the study or terminate the study altogether in order to protect the participants and ensure their safety.

DUE INFORMED CONSENT

Obtaining valid consent is critical in showing respect for autonomy since it present research volunteers the opportunity to choose to take part in research and to voluntarily expose themselves to the risks involved. It is the responsibility of the investigator to ensure that the informed consent document and procedure bears the valid elements that will assure that the volunteer is making an informed choice to participate in research. The elements of **capacity, competence, information** and **voluntariness** must be clearly demonstrated in the consent document. In reflecting on the subject of due consent, the **VanTx affair** reported in an Estonian newspaper in 1999 come to mind (Lemmens, 2001). As reported, research participants were brought into Switzerland from Estonia and Poland. These potential participants were mostly students recruited and sent to Switzerland to participate in clinical trials and receive payment for their participation. The company –VanTx –was a contract research organisation (CRO) situated in Bâle, and specialises in conducting phase 1 and bioequivalence/bioavailability trials in healthy volunteers for large international pharmaceutical companies.

This affair presented many unethical and troubling issues but of particular interest in this discussion is that the so-called volunteers **did not receive any information** about the trials in their mother tongue. On-site recruiters, simply explained that they would participate in drug trials and what the travel arrangements to and living conditions in Switzerland would be. Once in Switzerland, participants **received additional information in German, English and Russian;** languages not understood by many of the subjects. Participants signed a document considered by many of them to be a binding contract in English or German that they couldn't withdraw from the research nor seek compensation.

The ethical issue here is that they were not properly informed of their rights to withdraw from research at any time, to receive medical treatment and/or compensation for any adverse effects or to receive medical follow-up once they returned to their home country. This affair highlights the importance of acceptable recruitment processes that are an integral component of the consent process. It is particularly important that the recruitment process be evaluated by a competent research ethics committee.

CONCLUSION

Research volunteers are the people who come forward to aid society by exposing themselves to the risk of research and support the moral context of clinical research in being exposed to risks of harm for the potential benefit of future patients and society, (Miller, 2003). Since healthy volunteers have no chance to benefit from research participation, the risks to which they are exposed can be justified only by the value of the knowledge to be gained from their research participation.

Although it is expected that research involving healthy volunteers should be less likely to evoke ethical concern, yet, such research have features that can diminish prospective participants' ability to exercise free and informed choice and the level of uncertainty characterizing this form of inquiry makes subjects vulnerable to harm. To mitigate such vulnerability, appropriate risk benefit assessment should be conducted in line with the Declaration of Helsinki that "every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others" (WMA, 2 principle I.5). Also that, "medical research involving human subjects 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 subjects are healthy volunteers", (JAMA, 2000).

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