Good Clinical Practice in Nigeria-The way forward

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SUMMARY

Conduct of clinical research requires a high level of ethical and scientific standards which are enshrined in GCP guidelines. These guidelines contain requirements and responsibilities of the participants in the conduct of clinical research. The need for the protection of human participants in clinical research, which stems from unethical practices and fraud in the past, and also the need for a common standard in the conduct of research are some of the reasons for having GCP documents. Various GCP documents are written based on the ethical principles that are contained in the Helsinki declaration of 1964 by the World Medical Assembly. There is the need for Nigeria to produce her own GCP document with bias for our peculiarities or in the alternative adopt one of the existing GCP documents. Adherence to this document should be backed by appropriate laws and when this is done, integrity of studies done here in the country can be assured.

INTRODUCTION

Clinical research in the developed world is well regulated and compliance to high ethical standards in the conduct of clinical trials is mandatory. This is particularly so in areas where the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines are applied. GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects [1].

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Compliance with GCP guidelines ensures that the rights of human subjects in trials are protected, that clinical trials are conducted in accordance with ethical principles whose origins are in the 1964 World Medical Assembly Helsinki declaration and that data generated from clinical trials are credible[2].

Various laws and directives in many of the developed countries back adherence to ethical standards which are enshrined in the GCP guidelines. The Code of Federal Regulation (CFR) of the Food and Drug Administration (FDA) in the United State of America (USA) [3] as well as the European Union (EU) directives on clinical trials and GCP [4], [5] are some of examples of legal documents making compliance with ethical standards obligatory in clinical research. The code of federal regulation is also binding on investigators from countries outside of the USA seeking registration of their drug products in the USA.

In 1996 a big pharmaceutical company took advantage of the outbreak of cerebro-spinal meningitis in the Northern part of Nigeria to test an unapproved antibiotic on some Nigerian children in the city of Kano [6], [7]. 'Doctors without borders', who were helping out in the area then, conducted the study on behalf of the company. The study subjects were not aware they were taking part in a study, no informed consent was taken and no ethical approval was sought [7]. The study led to the death of five children who took the study drug [6]. Subsequent to this incident, an American newspaper in one of its article wrote that, giving a situation where there is abundance of subjects' population and minimal oversight, big pharmaceutical companies test their products abroad in order to get to the market faster [7]. African research populations are vulnerable to manipulation and coercion, hence the need to have regulations in place to protect human subjects in research.

HISTORICAL BACKGROUND

Ethics in clinical research has a long and rich history of development. Past abuses of human subjects in clinical research as well as past cases of negligence and outright fraud in research have led to its evolution. It is estimated that 1 in 100 000 severe cases of documented fraud occurs per year among scientists, also 1 in 10 audit of clinical research provides a finding of major deviations from protocols [8]. The recent case of falsification of data by a South Korean researcher involved in the stem cell cloning research is still very fresh in our memory [9]. Fraud in clinical research ranges from sloppiness (honest error in recording of data, may be due to negligence), falsification (deliberate altering of data) to outright fabrication of data (producing data that did not exist). Gift authorship is also regarded as fraud and unethical in clinical research.

In 1937 there were reported deaths of 107 people, mainly children following the use of sulphanilamide elixir [10]. The drug is an antibiotic that was widely available and recognized at the time. These deaths occurred following the formulation of a liquid form of the antibiotic for use in children. The manufacturer dissolved the drug in diethylene glycol, a chemical closely related to antifreeze, to produce the elixir form of the drug. The elixir was then used in children without any prior pre-clinical evaluation to discover its effect in humans. The food, drug and cosmetics act of 1938 by the USA congress was enacted as a direct consequence of this incidence [10].

In 1947 the Nuremberg code came into effect . This code came about following abuse of war criminals that were coerced into take part in a clinical research during the period of 1946-1949. No consent was obtained from these subjects. The Nuremberg code emphasized for the first time the principle of informed consent [12]. Other clauses in the code include; need for pre-clinical animal study, protection of study subjects from harm, freedom of subject to withdraw from participation in studies at any time, need for qualified investigators, need to stop treatment if harm occur, anticipation of scientific benefit, no intentional death or suffering resulting from the study and finally benefit must outweigh the risk [11].

In the 1950s and 1960s the use of thalidomide to treat nausea in pregnant women resulted in the birth of more than 10, 000 phocomelics [13]. There was no pre-clinical evaluation of possible teratogenic effect of the drug in animal models prior to its approval for marketing. In addition, the neurological side effects of the drug which were observed during its clinical evaluation were ignored. Kefauver-Harris amendment of the food, drug and cosmetics act of the FDA was enacted following the disaster [14]. This amendment required the provision of efficacy data as well as greater safety data for new drug application. In many of the European countries affected by the thalidomide disaster, regulations requiring registration of medicinal products were enacted [13].

In 1964 at the 18th World Medical Assembly in Helsinki, Finland, a declaration of ethical principles to serve as a guide to physicians and other participants in medical research involving human subjects was made [2]. The declaration is however not legally binding on researchers but meant as a guide.

The Tuskegee experiment of 1932-1970 was another sore point in the history of ethics in clinical research [15]. The study had the approval of the USA Department of Public Health. Poor black men suffering from syphilis were regularly examined and had the progress of their disease documented without any form of intervention despite the availability of a known treatment (penicillin) for the condition [15]. At least 40 men lost their lives as a direct consequence of this study [15].

In 1974, the National Research Act of the United State of America was signed into law, thereby creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research [16]. 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 subjects and to develop guidelines, which should be followed to assure that such research is conducted in accordance with those principles [16]. The Belmont Report of 1979 attempted to summarize the basic ethical principles identified by the Commission in the course of its deliberations. The

basic tenets in the report can be summarized into three basic issues; respect for persons, beneficence and justice [16].

THE CURRENT STATE

The gold standard for Good Clinical Practice is the ICH-GCP. The European Union, the United States of America and Japan jointly produced this document with inputs from Canada, Australia, the Nordic countries and the WHO [1]. The main objective of the guideline is to produce a unified ethical standard for countries in these areas in the conduct of clinical research. This was to ensure mutual acceptance of clinical data by regulatory authorities in these areas. Compliance with the guideline is obligatory when generating clinical trials data that are intended for submission to the regulatory authorities in the areas where the guideline is adopted.

The Code of Federal Regulation in the US, the EU directives in the EU zone as well as various local statutes in many countries of the developed world give legal backing to compliance with GCP in the conduct of clinical research [3], [4], [5].

The key concepts of the ICH-GCP can be summarized into three key elements; accountability, responsibility and reproducibility. The document spelt out responsibilities and obligations for all that are involved in the conduct of clinical research. Major players in the conduct of clinical research include the Institutional Review Board/Independent Ethics Committee (IRB/IEC), investigators and sponsors [1].

The IRB/IEC has the main responsibility of safeguarding the rights, safety and the well being of all trial subjects. The Ethics Committee is an independent body constituted of medical, scientific and non-scientific members, whose responsibility it is to ensure the protection of the rights, safety and wellbeing of human subjects involved in clinical trial [1]. The board is expected to review and approve the trial protocol as well as the inform consent document (ICD). It should ensure that the investigator is suitably qualified to conduct the study and that the study is scientifically sound.

Investigators should be qualified by education, training and experience to assume responsibility for the proper conduct of the clinical trial [1]. An investigator is the person responsible for the conduct of clinical trial at the trial site. If the clinical trial is conducted by a team of individuals at a site, then the investigator is the leader of the team and may be called the Principal Investigator (PI) [1]. They should conduct the trial in compliance with the trial protocol and must be familiar with the appropriate use of the investigational products being tested. The investigator should have sufficient time, adequate number of qualified staff and adequate facilities for the foreseen duration of the trial in order to conduct the trial properly and safely.

Sponsors are responsible for implementing and maintaining quality assurance and quality control[1]. Sponsor is an individual, company, institution or organization which takes responsibility for the initiation, management and/or financing of a clinical trial [1]. They employ staffs for monitoring of study; engage independent auditors to ensure the integrity and quality of the data generated as well as compliance with GCP. The sponsor can also contract any or all its trial related responsibilities out to Contract Research Organization (CRO).

WHO-GCP guideline is another GCP document; it sets a globally applicable standard for the conduct of biomedical research in human subjects [17]. It was prepared based on provisions in the ICH-GCP; it however differs in its content and emphasis. The guideline is a basis for mutual recognition of clinical trial data generated within countries that subscribe to the document. It is a practicable administrative tool for use by the WHO member states for the purpose of harmonization of national standard in clinical research. The guideline is not meant to challenge or replace any existing national regulations or requirements but rather provides a complimentary standard. In countries where there are no already existing national regulations or requirements, the guideline may be adopted in part or in whole as the basis for the conduct of clinical trials.

The declaration of Helsinki is the reference for the development of these various GCP documents. It should be adhered to and respected by all parties involved in the conduct of clinical trials. The current version of the declaration is the

acceptable version [2]. Any departure from the declaration must be justified and stated in the trial protocol for the approval of the IRB/IEC. There have been several amendments to the original version of the Helsinki declaration; the most contentious amendment bothers on the issue of use of placebo-control in studies. The declaration as amended states that new treatment should be tested against the best current standard, and that placebo or no treatment can only be used when no known proven treatment exist [2]. There is a note however stating exceptions to the use of placebo. One is that for compelling scientifically sound methodological reasons even when a standard treatment exist the use of placebo can be allowed. Also, when treatment is being investigated for minor conditions and subjects in trials will not be subjected to any additional risk of serious or irreversible harm, placebo can use as control.

CONCLUSION

Nigeria as the most populous black nation in the world is a big market for the pharmaceutical industries. The way forward for Nigeria will be the adoption and ratification of a GCP document with appropriate modifications to suit our peculiarities. This can be done by strengthening the act setting up our National Agency for Food and Drug, Administration and Control (NAFDAC) to make compliance with GCP obligatory in clinical trials of drugs meant for marketing and registration in the country.

There is a need to encourage more drug trials in the country, particularly drugs meant for registration.

Our ultimate aim should be to meet the ICH-GCP standard. When this is done, big pharmaceutical companies will be willing to do more studies here because such studies will be internationally acceptable since high ethical and scientific standard will be ensured.

Nigeria already has trained man power in many areas of the medical sciences, but what we lack are the infrastructures, enabling environment and adherence to high ethical and scientific standard. When these are put in place we can be assured of more support from the international scientific world as a lot still need to be done in many area of medical research. We can start now.

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