

An Assessment of the Knowledge of Clinical Researchers In Nigeria About the Responsible Conduct of Clinical Research.

Kayode Julius , Adebayo

Chemical Pathology department, Faculty of Clinical Sciences, College of Medicine,

Ambrose Alli University, P.M.B 14, Ekpoma. Edo State, Nigeria

e-mail: kjadebayo@yahoo.com

NB, this work was done as a student of the Department of Clinical Research and Regulatory Administration of the School of Professional Studies, Northwestern University, Chicago Campus, IL. USA.

The research is financed by the author

Abstract

An assessment of the knowledge of clinical researchers in Nigeria about the responsible conduct of clinical research has become important because of the growing need of same. This study assessed the knowledge of clinical researchers in Nigeria about responsible conduct of research. This has become necessary because of the difficulty faced in finding a local, well-trained work force to conduct clinical trials in the developing world. This study surveyed clinical researchers in Nigeria to determine their level of clinical knowledge within a specific arena of Good Clinical Practice (GCP): the responsible conduct of research. This is a pilot study and the sample size was 50. Subjects were medical researchers trained in Nigeria and currently involved in clinical research. These were drawn from academia, research institutes, teaching hospitals, regional and state hospitals and specialist treatment centers all over the country. After getting the Institutional Review Board [IRB] approval from Northwestern University, Chicago, an introductory email with a link to the 5 minute survey on surveyMonkey was sent to clinical researchers in Nigeria. Two subsequent reminders were sent one week apart. There were 14(61%) males and 9(39%) females. Subject ages ranged between 30 and 69 years with the majority between 40 and 49 (43%) years. Most respondents (78%) graduated from medical schools more than 20 years ago. The respondents attended medical schools all over Nigeria; South West (39%), South South (22%), North Central (26%) and South East (13%). Almost all of the respondents, 21 (91%), volunteered that they have completed a formal training in responsible conduct of research. Locations of RCR training included medical school, postgraduate residency training and teaching hospital. Clinical researchers in Nigeria have some knowledge of RCR but more needs to be done in the area of training. There is a great need for the incorporation of training modules in RCR in the curriculum of students at undergraduate and graduate levels in Nigeria. A follow up study is recommended to more precisely determine the level of knowledge of clinical researchers in Nigeria about Responsible Conduct of Research.

Keywords: responsible conduct of research (RCR) , GCP, Nigeria, clinical Research.

1. Introduction

The subject of responsible conduct of research (RCR) is an interesting one to anyone involved in the conduct of research with the intention of adding to knowledge and or helping to alleviate the suffering of patients. Getting new drugs to the market, testing and marketing new devices, or even looking into the effectiveness and safety of products in the market all need studies to be conducted in a responsible way.

The importance of science and technology has grown tremendously in the 20th century. Today, most aspects of our life are touched by information and technologies resulting from research. The support of research using public funds has grown substantially, hence the growing demand and concern about how research is conducted. Public funds support roughly one-third of all research and development (R&D) in the United States of America [USA] and half of basic research (Dorsey ER, et al, 2010). Thus, many researchers spend much time working for the public. As public servants and professionals, researchers are obliged to conduct their research in a responsible way.

Simply put, responsible conduct of research (RCR) is good citizenship applied to professional life. This means that all processes and stages involved in the conduct of research must be performed in a responsible way so that public funds are not wasted (<http://ori.hhs.gov/education/products/RCRintro> 2014).

The situation in the USA is similar to that in most parts of Western Europe and Canada. The government is very involved in the regulation and financing of clinical research. Vetting of results from private and institutional researchers is being done.

When it comes to the developing countries, like Nigeria, the story is different. Most research funding in Nigeria is not from the government (Bello, TO, 2012) . National rules on RCR are still evolving. RCR training and regulation is still in the infancy stage. Thus, individual researchers and corporate sponsors have a big role to play in the research. Many researchers, if not most, tend to be controlled by their sponsors.

1.1 History of RCR

Responsible conduct of research has a long and enduring evolution. RCR came into being and is closely associated with research ethics following the florid and horrific cases of abuse of human subjects in research. Fraud in clinical research ranges from negligence or error in data recording, falsification (data alteration intentionally) to outright fabrication (making up a data set that never existed) fraud. According to Marshall, about 1 in 100,000 severe cases of documented fraud occur per year among scientists, also 1 in 10 audits of clinical research provide a finding of major deviations from protocols (Marshall E, 2000).

A key 20th century example of irresponsible conduct of research is the Tuskegee Syphilis Study, sponsored by the U.S. Department of Health (Thomas, SB, and Quinn, SC. 1991). The effects of untreated syphilis were studied in 400 African American men. Researchers withheld treatment even when penicillin became widely available. Researchers did not tell the subjects that they were in an experiment. The subjects were told that

they were being treated for “bad blood” and this went on from 1932 to 1972! The most appalling aspect of this case was that the study had the approval of the US Department of Public Health. What a paradox, this is the department vested with the healthcare of these individuals. Research regulations and subject safety protection evolved as a result of a variety of ethically questionable research practices.

1.2 Food, Drug and Cosmetic Act

Some of the survivors of the 1937 sulphanilamide elixir study (www.fda.gov/oc/historyoffda/section2.html), where 107 people-- mainly children-- died after diethylene glycol was used to produce the elixir, are still telling the story. The problem here was that no clinical trials were performed to establish the elixir’s safety. Although sulphanilimide was in use as an antibiotic in adults, the diluents--diethylene glycol-- used in making the elixir, were never tested before being introduced into the market for human use. This unfortunate incident led to the 1938 Food, Drug and Cosmetic Act of the US.

1.3 Nuremberg Code

The excesses and despicable acts of German scientists towards prisoners in their infamous concentration camps during the Second World War (1939 – 1945) are still fresh in our memory. The Nuremberg code came into effect in 1947 following the protracted trials of the notorious Nazi doctors/researchers from 1946 - 1949. Subjects’ rights issues included coercing subjects to participate, lack of a scientific protocol, and inability to withdraw from the study. As later stipulated in the Nuremberg code, this was heinous and flagrant abuse of human rights because it was not free from “the intervention of element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion”(Shuster E, 1991). The Nuremberg code introduced the concept of informed consent. It also stressed other subjects’ rights tenets that are common today: a) the need to engage in pre-clinical animal studies; b) protection of study subjects from harm; c) freedom of study subjects to withdraw from participation at any time; 4) the unquestionable competence of the researcher; 5) no intentional death or suffering resulting from the study; and 6) the fact that benefits must outweigh the risk. According to Shuster the Nuremberg code has changed the way clinical research is being conducted *for good* forever.

1.4 FDA Oversight

In the 1950s and 1960s thalidomide was used to treat pregnant women for nausea. The phocomelia that resulted from its use again illustrates the need for exhaustive and rigorous clinical research before the introduction of drugs to the market. The use in the US was delayed by the FDA under the watchful eye of Dr Frances Kelsey because of the neurologic side effects (Kelsey FO, 1938). More studies were ordered to further understand the causal or casual relationship with peripheral neuropathy. When phocomelia and amelia were reported in Europe, the ban on use in pregnancy in the US was issued. Despite this tragedy, thalidomide is still being used worldwide today for the treatment of leprosy and multiple myeloma with extreme caution in women (Kim JH, Scialli, AR 2011). This shows that the problem was the haste in introducing it to the market.

1.5 Declaration of Helsinki

The World Medical Assembly met in Helsinki, Finland, in 1964 and issued a declaration of ethical principles to serve as a guide to physicians and others who participate in medical research involving human subjects (www.wma.net/en/ 2014). Although this is not a law, it has done much to improve the responsible commission of medical research. The European Union, US and the World Health Organization [WHO] have been able to expand on this provision to write laws and codes of ethics regulating responsible conduct of research.

1.6 National Research Act

In the US, the National Research Act was signed into law in 1974. This enabled the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (www.hhs.gov/ohrp/humansubjects/guidance/belmont). In 1979, the Belmont report summarized the tenets of good and responsible clinical research as having three fundamental concerns; respect for persons, beneficence and justice.

1.7 The Nigeria case

Responsible conduct of research in Nigeria is comparable to that in most third world countries. However, concerns are growing and training in research ethics and research regulation is off to a good start. Research misconduct is usually resolved at the institutional level. Celebrated cases are usually supplanted by the powers that be if such a researcher is of the same tribe, same or favored political party, or the individual has money to throw around. The bias here is in favor of anything other than merit or science.

In 2000, Dr Jeremiah Abalaka, a surgeon, shocked the nation with his claim of finding a cure for HIV/AIDS (www.nigeria-aids.org/content). This was found to be a false claim and nothing happened to him despite making a great deal of money from patients far and near.

There was a case I witnessed as a medical student in one of the best medical schools in Nigeria. Two of my lecturers accused one another of plagiarism and they both got fired. Each went to the far flung corners of the country and got reabsorbed into the University system after some time. The plagiarism charges were a result of each of them publishing research in a foreign language, largely understood only by the publishing researcher, until the publication was translated.

In the past, the problem of RCR in Nigeria resulted from ignorance of the existence of RCR. Dwindling local financing for clinical research, the need for researchers to network and the desire to benefit global investment in clinical research is currently fueling the craving to align with the rest of the world as far as RCR is concerned. Training has been identified as a strategy for addressing the RCR needs of IRB/IECS, sponsors and researchers. According to Ajuwon and Kass (2008), training helps in ensuring the protection, safety and integrity of clinical research in at least three ways. First, formal and educational updates in research ethics open the researchers to new and emerging trends in clinical research. Second, training can provide skills for

dealing with issues concerning RCR. Finally, training creates a platform for researchers in developing countries to contribute to the ongoing global debates in RCR.

It is important to note that most of the universities, research institutes and teaching hospitals in Nigeria do not have any repository or database of clinical research carried out in such facilities. This has resulted in the duplication of projects by students and lecturers/faculties thereby wasting human and material resources. For instance, a student could place their name on a completed project that is kept in a departmental library and then successfully re-submit the same project as new in another arena. Consultants/attending doctors, resident doctors and other medical researchers may be unaware of previous work and go over the same or too similar research topics time and again. This individualistic approach is partly due to mismanagement of intellectual property rules. The result is the production of many, similar single author publications which have less oversight than multi-author projects would.

The European Union, US and Japan jointly produced a document with contributions from Canada, Australia, the Nordic countries and the World Health Organization. This document, The International Conference on Harmonisation-GCP, is the gold standard for good clinical practice. It guides researchers in member countries to use a unified ethical standard in the conduct of clinical research. This document also paved the way for the acceptance and exchange of data generated by researchers working in member states or nations. Compliance with this document will ensure that the data thus generated can be submitted to authorities in member states for consideration when conducting clinical trials. This has helped in reducing the time needed for bringing drugs and devices to the market since trials can be done concurrently in member states instead of serially. Cost is also saved since trials can be done in any of the member states and adopted by other states after verification.

1.8 WHO-GCP [World Health Organization- Good Clinical Practice Guideline]

The World Health Organization has set up a document, World Health Organization-GCP guideline (<http://apps.who.int/medicinedocs/pdf/whozip13e>), with global applicability standards for the responsible conduct of clinical trials. This document is meant to compliment national standards in member states and it is aimed at encouraging acceptance of data produced in member states. It serves a unique purpose for member states that are not able to formulate their own national document where it can thus be adopted, customized and implemented.

2. Methods

In order to answer the research question, the RCR curriculum of Nigerian medical schools was reviewed and clinical researchers in Nigeria were surveyed to determine their level of clinical knowledge within a specific arena of Good Clinical Practice (GCP): the responsible conduct of research.

2.1 Sample:

The goal for this pilot study was to survey a sample of 50 Nigerian clinical researchers. In order to meet that goal, 90 potential subjects were contacted via e-mail. This was a sample of convenience drawn from the membership of the association of pathologists of Nigeria (ASSOPON). The author belongs to this network and this network represents medical researchers trained in Nigeria and currently involved in clinical research who work in academia, research institutes, teaching hospitals and state/regional hospitals and specialist treatment centers all over the country.

2.2 Survey:

There were 28 items in the survey which included question on basic demographic information (sex, region of medical training, training institution), scientific background (publications, role in clinical research), RCR training, and assessed the subjects' knowledge of responsible conduct of research (see Appendix A). Finally, the survey gathered subjects' attitudes about the need for RCR, availability of RCR training in the medical school curriculum or residency training program, and quality of local educational opportunities on responsible conduct of research.

A multi-step process was utilized in sending out the survey. After the e-mail contact information was obtained from the ASSOPON list-serve, an introductory e-mail was sent to all potential subjects. The e-mail introduced the author, briefly described the survey and provided a survey monkey link. SurveyMonkey was used since it is familiar and accessible to the subjects as well as easy to use and allows for the identification of non-responders. Two reminders were sent to subjects (at one week and two weeks).

2.3 RCR curriculum search:

Current educational opportunities for GCP training were assessed by going through the websites and curriculum of all 25 fully accredited medical schools in Nigeria. The factors/criteria looked for on the websites included listing of IRB/ERC on the University and or the College of medicine websites, course(s) on responsible conduct of research, any statement on RCR, and if RCR is incorporated in any other course. The presence/availability of any factor of interest was assigned a "Yes" while the absence attracted a "No".

2.4 Human Subject's Safety:

The proposal, protocols, questionnaire, introductory and follow up emails associated with this survey were forwarded to The Northwestern University IRB for review and the survey commenced only after the IRB approval was obtained. As a requirement, I had to train with and pass relevant sections of the Collaborative Institutional Training Initiative [CITI] training modules.

Informed consent for the survey was obtained when each respondent entered the survey link. The informed consent appeared as the first page of the survey, in SurveyMonkey. In order to begin the survey the

respondent needed to agree to participate, however, if the respondent chose not to consent, the survey automatically ended.

3. Results

Only 23(20.7%) of the 90 subjects contacted responded within the two week survey period. The results were analyzed despite the poor response because this is a pilot study. There were 14(61%) males and 9(39%) females. Subject ages ranged between 30 and 69 years with the majority between 40 and 49 (43%) years.

3.1 Description of Respondents:

Most respondents (78%) graduated from medical schools more than 20 years ago. The respondents attended medical schools all over Nigeria; South West (39%), South South (22%), North Central (26%) and South East (13%). Figure 1 shows the responses by geopolitical zone. The knowledge of RCR as measured by the four key questions [6 &7] on the questionnaire correlates positively with the length of years in clinical research and the number of scientific publications. Three respondents have over 50 publications and over 20 of those publications in international peer review journals, they had a score of 100%. Principal investigators and co-investigators had a score of hundred and the scores declined thereafter.

3.2 Knowledge of RCR

Of the 23 respondents, all (100%) agreed that responsible conduct of research is necessary. Twenty-two respondents (95.7%) agreed that responsible conduct of research prevents plagiarism. Sixteen respondents (69.6%) agreed that self plagiarism is possible, six (26.1%) were not sure and only one (4.3%) respondent disagreed. Eighteen respondents (78.2%) agreed that RCR involves authorship issues while five respondents (21.7%) were not sure and no disagreement.

3.4 Scientific background, publications, role in clinical research and RCR training

Of the 23 respondents, 2 (8.7%) have been in clinical research for 21-30 years, 3 (13%) have been in clinical research for 11-20years and 18 (76.7%) have been in clinical research for 1-10 years. The usual roles of the respondents are as principal investigators, 9 (39%), co-investigator 10 (43.4%), clinical research associate/monitor, 2 (8.7%) while mentoring and laboratory support accounted for 8.7%. The total number of scientific publications were 1-10 for 7 (30.4%) respondents, 11-20 for 6 (26.1%) respondents, 21-30 for 5 (21.7%) respondents, 31-40 for 2 (8.7%), and greater than 50 publications for 3 (13%) respondents.

Two questions measured the how important respondents believe RCR to be (RCR is necessary and RCR prevents plagiarism). Two additional questions assessed the respondents' knowledge of RCR (Self-plagiarism is possible and RCR involves authorship issues). The result is as shown in Table 1.

3.5 Website Findings

Of the 25 fully accredited Nigerian medical schools as of September, 2014, none had any information online regarding RCR. They have no RCR statement and have no online information about where or how clinical research can be conducted. Of these 25, 14 (56%) are owned by the Federal government, 9 (36%) are state owned while 2 (8%) are privately owned.

4. Discussion

My initial literature review results have confirmed that research education offerings and research oversight in developing countries is so minimal that the quality of clinical research in these areas is still at an early stage. Encouragingly, researchers in the developing world are clamoring for a change. They are expressing the need to embrace GCP and responsible conduct of research as applicable in the developed world (Adeleye OA, Adebamowo CA(2012).

This study is one of the early studies in Nigeria aimed at assessing the level of knowledge of researchers in the areas of responsible conduct of research.

The survey itself could also be improved. It would be very useful to obtain better assessment RCR knowledge from respondents. In order to both assess current knowledge and provide something of value to respondents, the survey could be combined with a training module. A pre test, training module and post test format could be used to assess knowledge, provide training and also assess the effectiveness of an online or video training.

Expanding the study to other physician groups outside of pathology would be beneficial in both garnering a larger response rate and also assessing the understanding of RCR among all clinical researchers in Nigeria.

5. Conclusion

Clinical researchers in Nigeria have some knowledge of RCR but a great deal needs to be done in the area of training. Getting new drugs to market, testing and marketing new devices, or even looking into the effectiveness and safety of products in the market all need studies to be conducted in a responsible way.

Next Steps:

Moving forward, the following consecutive steps to address RCR training and adherence needs are suggested:

1. Post and publicize the Nigerian RCR guidance approved in 2007
2. Implement a multi-faceted training approach to include:
 - a. RCR info & sources (CITI) on medical school web-sites
 - b. RCR in the curriculum of medical schools
 - c. RCR in the requirements for fellowships
 - d. RCR training as a requirement for IRB certification



References

Abalaka: where the press go wrong <http://www.nigeria-aids.orgcontent.cfm?2c> [April 10,2014 Online]

Adeleye OA, Adebamowo CA(2012). Factors associated with research wrongdoing in Nigeria. *J Empir Res Hum Res Ethics*. December; 7(5): 15 -24.

Ajuwon AJ, and Kass N. Outcome of a research ethics training workshop among clinicians and scientists in a Nigerian University. *BMC Medical Ethics* 2008; 9:1<http://www.biomedcentral.com/1472-6939/9/1>

Bello, TO: Funding for Research in Science and Technology in Nigeria Universities: The Gender Perspective. *Journal of Emerging Trends in Educational Research and Policy Studies (JETERAPS)* 2012: 3 (1): 34-38.

Dorsey ER, et al (2010). Funding of US biomedical research 2003-2008. *JAMA* 2010,303;137-143. <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html> [April 8, 2014 online]

FDA. History of the FDA: The 1938 Food, Drug and Cosmetic Act. [Http://www.fda.gov/oc/historyoffda/section2.html](http://www.fda.gov/oc/historyoffda/section2.html)[2014]

<http://apps.who.int/medicinedocs/pdf/whozip13e/pdf> [April 9, 2014 online]

<http://ori.hhs.gov/education/products/RCRintro/0frontis/3frontis.html>[2014]

Kelsey, FO . Thalidomide update: regulatory aspects. *Teratology* (1988)38; 221-226.

Kim JH, Scialli, AR. Thalidomide: The tragedy of birth defects and the effective treatment of disease. *Toxicological sciences* (2011) 122(1), 1- 6.

Marshall E. Scientific Misconduct: How prevalent is fraud? That’s a million dollar question. *Science* 2000; 290(5497); 1662 – 1663.

Shuster E. fifty Years Later: The Significance of the Nuremberg Code. *N Engl J Med* (1997); 337:1436-1440 November 13, 1997DOI: 10.1056/NEJM199711133372006

Thomas, SB, and Quinn, SC. The Tuskegee Syphilis Study, 1932 to 1972: Implications for HIV Education and AIDS Risk Education Programs in the Black Community. *Am J Public Health* 1991; 81: 1498-1504.

World Medical Association. DECLARATION OF HELSINKI.

Ethical Principles for Medical Research Involving Human Subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the: 59th WMA General Assembly, Seoul, October 2008 <http://www.wma.net/en/30publications/10policies/b3/17c.pdf> [April 8, 2014 online]

Table 1. Core RCR Question

Role in Clinical Research	Core RCR question score
Principal Investigator	100
Co-Investigator	100
Principal Investigator	100
Co-Investigator	100

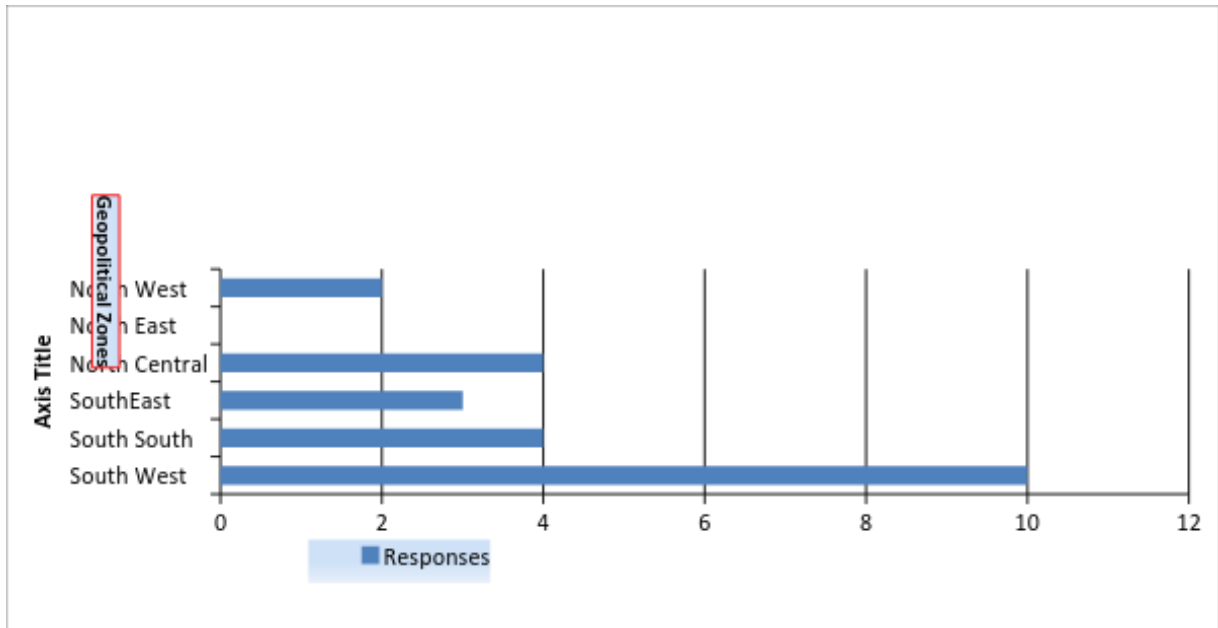


Figure 1. Respondent medical school training location by Geopolitical zone