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# Current Review of Medical Research in Developing Countries: A Case Study from Egypt

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Sherif M. Shehata, Nehal M. ElMashad and  
Azza M. Hassan

Additional information is available at the end of the chapter

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## Abstract

It is amazing to see how medical science has progressed. Medical research is now cross-national and cross-cultural, the relentless progress of globalization poses complex ethical questions for those wishing to do medical research in developing countries. In developing countries, poverty, endemic diseases, and a low level of investment in health care systems influence both the ease of performing and the selection of trials that can benefit the people of the countries. In this chapter, we present an overview of medical research situation in developing countries with critique of different clinical trials that was conducted in Egypt after review. Egypt has 41 universities and 94 health related medical schools. There are 24 faculties of medicine with up to 34 departments in each. Clinical research is an essential mandate for getting Master, Doctorate Degrees, and for promotion of faculty members. In Egypt, the Profession Ethics Regulations issued by the Ministry of Health (MOH) No. 238/2003 was endorsed and maintained in Law 71/2009. Beside these regulations, more than 56 Institutional Review Board (IRB) have been registered. The Egyptian Network of Research Ethics Committees (ENREC) was created in 2008. Yet, in the absence of robust legislative constraints, there is no clear way to avoid violations. Our experience in Tanta Faculty of Medicine is also highlighted in this chapter.

**Keywords:** medical research, medical ethics, developing countries, Egypt, Tanta Faculty of Medicine, Tanta REC

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## 1. Introduction

It is amazing to see how medical science has progressed. It has only been a hundred years and the world has gone from the discovery of penicillin to the complete sequencing of the human genome. This is the *“Medical Research.”*

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Many researches are driven by economic or academic interests that may or may not reflect the needs of the host country. One critic of such trials is the need to test new drugs for malaria, sleeping sickness, and Chagas disease that people in poor countries suffer from rather than on diseases of interest primarily to the developed nations.

There is also the delicate matter of double standards, which highlights the need to develop an ethical model for research and training partnerships between developed and developing countries employing an approach with long-term advantage for the latter or both partners at least in an equal manner.

## 2. Realities of medical research in developing countries

### 2.1. Historical background

The past 20 years have seen a considerable shift in the location of clinical drug trials sponsored by transnational pharmaceutical companies (TNCs) being conducted in low- and middle-income settings [1]. One of the primary obligations of the Declaration of Helsinki (DH) is to promote human well-being over the interest of science and society. According to DH, any medical study should provide every participant with the best proven diagnostic and therapeutic method [2]. The primary ethical commitment would be obtaining rapid, nonargued answers that may make researchers cross the line that forbids treating human subjects as a means to an end, leaving nothing to protect patients from underestimating their dignity, rights, and safety for the sake of research goals [3].

One of the great challenges in medical research is to conduct clinical trials in developing countries that benefit the citizens of these countries. After the textbook example of the unethical 40-year nontherapeutic study of 400 African American sharecroppers in “the Tuskegee Study of Untreated Syphilis” (TSUS), ethical concern stood on its head and led to the overhauling of federal guidelines for health research [4]. These reforms, however, do not extend to health studies conducted outside the United States [5].

Ethical review committees are present in developing countries in the form of research institutes or other scientific panels [6]. However, the reality is that these panels need to be independent and able to review clinical trials without prejudice. Also, the characteristics of many developing countries, which include population afflicted with life-threatening endemic diseases, poverty, and a low level of investment in health care systems, affect both the ease of performing trials and the selection of trials that can benefit the populations of the countries. Conflict of interest of physicians/researchers from developing countries is a detrimental factor in research bias. There are also some structural problems including the fact that operations of pharmaceutical research companies are not adequately controlled or authorities seem unwilling to address unethical drug testing [7].

There appears to be a general retreat from the clear principles enunciated in the Nuremberg Code and the DH as applied to research in the third world. Angell in 1997 wondered, “Why

is that?!" He attributed it to the differences in local standard of care or variation in diseases and their treatments in those regions, so that information gained in the industrialized world has no relevance making it a must to start from scratch [3].

## 2.2. International situation in developing countries

Indeed, the scale of the problem is unknown, because it cannot be estimated how many unethical clinical trials escape public attention and therefore remain unnoticed. Starting in 1996, TSUS-like scenario occurred in Pfizer's controversial Trovan clinical trials that took place in Kano over 200 persons, mostly children [8]. The new quinolone was tested without parents' informed consents; patients were unaware of the experiment and without an ethical review committee's approval of the trial in advance. Out of 190 children that were enrolled in the trial, five receiving the drug died while others suffered brain damage and paralysis. A panel of Nigerian medical experts reported that the trials had been illegal and exploitative and violated Nigerian law, the DH, and the UN Convention on the Rights of the Child. However, Pfizer denied that the drug trial was unethical [9].

One of the major examples of the Tuskegee-like trials in the third world is the regimens to prevent the vertical transmission of human immunodeficiency virus (HIV) [10]. According to CDC, 18 randomized, controlled trials of interventions to prevent perinatal HIV transmission were identified until 1997, 16 were conducted in developing countries in Côte d'Ivoire, Uganda, Tanzania, South Africa, Malawi, Thailand, Ethiopia, Burkina Faso, Zimbabwe, Kenya, and the Dominican Republic [11].

These trials involved a total of more than 17,000 women. In 15 of these trials, some or all of the patients were not provided with clearly effective zidovudine antiretroviral drug as they employ placebo-treated control groups. Failures to get patients' consent about changes in the experiment, administering wrong doses, serious problems in record keeping, delayed and under-reporting of fatal and life-threatening problems, nondisclosure of thousands of side effects and adverse reactions, not following procedures for divulging Serious Adverse Events (SAEs), and destroying an early copy of the research reports are part of the violation of guidelines [10, 12].

Another same example was the dramatic Cariporide clinical trial applied in the Naval Hospital in Buenos Aires, Argentina to protect against heart damage after cardiac insult. Patients' consents were either faked or the patients did not know its contents. Thirteen patients died and at least three of them were considered murders. Data in medical records were changed and key documentation disappeared [13]. Although before 2005, the Schedule Y of the Indian Drug and Cosmetic Act prohibited clinical trials in India of drugs developed outside the country before Phase II trials were completed abroad, a review revealed that some illegal studies were conducted in 1999–2000. Phase III trials involving cilansetron, a new molecule of Solvay Pharmaceuticals for treatment for diarrhea from irritable bowel syndrome (IBS) [14], Pfizer's zoniporide trial that control perioperative cardiac events [15], nordihydroguaiaretic acid (NDGA) as treatment for oral cancer, and Otsuka's cilostazol trials for treatment of intermittent claudication were tested before the required animal experiments had been completed and serious adverse events were not reported [15, 16].

Between 2002 and 2006, the number of trials to compare antiretroviral standard continuous and intermittent therapies was conducted in Africa. The Development of Anti-Retroviral Therapy (DART) trial had recruited 3300 volunteers in Uganda and Zimbabwe [17]. Unfortunately, unethical trials continue to be conducted. One recent trial in India, reported in *The Lancet* in 2014, evaluated human-bovine (116E) vaccine for preventing a very common, potentially life-threatening viral infection “rotavirus” [18]. Two rotavirus vaccines have been available for the past decades that were proved to be highly effective in preventing rotavirus-induced gastroenteritis and the need for hospitalization. One of the unfair examples, despite the availability of these vaccines, more than 2000 children in the Indian trial received placebo injections of salt water rather than one of the available effective vaccines in a clinical trial funded by multiple private and government sources and enrolled approximately 6800 infants between 2011 and 2012 [18].

The central ethical question should be: why has not the successful intervention that is currently used as a matter of course in Western countries become the standard of care worldwide? Clinical trials have become a big business with many studies done in developing countries, as it is necessary to do quick work with minimal obstacles. Poverty and ignorance play a role in commercial industry like this. This does not suit the standards of the sponsoring countries and puts us not very far from Tuskegee even after more than 80 years [19]. This is a big concern for all of human race. Like Lurie and Wolfe [10], we need to redouble our commitment to the highest ethical standards, no matter where the research is conducted, and sponsoring agencies need to enforce those standards, not undercut them.

### 2.3. The case of Egypt: strength versus weakness

The contract research organization (CRO) Quintiles even recently advertised Russia, Turkey, and the Middle East and the Northern Africa MENA region as the “new darlings” in the world of biopharmaceutical sales [20]. According to the *ClinicalTrial.gov*, a service of the U.S. National Institute of Health (NIH), 1234 clinical trials were conducted in Egypt with the number of clinical trials nearly tripling between 2008 and 2011 making Egypt second only to South Africa on the African continent in terms of the number of TNC-sponsored studies [21, 22]. Based on the registry of clinical trials (CTs) in Egypt, treatment was the most common study purpose followed by prevention. Combined safety/efficacy was the most common endpoint followed by efficacy alone. For interventional studies, the most common intervention was drug use followed by procedure. The most common study phase was phase 3 followed phase 4 and phase 2. However, the output of the big number of health professionals and faculty members is definitely more than the registered studies, which, may be related to absence of Egyptian national trial registry and the national mandates for trial registration [23].

In February 2016, 21 international pharmaceutical and biotechnology companies were sponsoring active drug trials in Egypt. The two Swiss giants Novartis and Roche carried out the lion’s share of trials. These trials took place at 131 sites spread over 9 cities in Egypt. Unsurprisingly, the majority was in Cairo (75), followed by Alexandria (31)—together accounting for about 81% of all sites. Over half of all international active drug studies in Egypt are cancer trials, followed far behind by infectious diseases (10%) and metabolic disorders (10%) [21].

An attractive research infrastructure, a fast-growing and largely treatment-naïve population, a mosaic panel of research areas, and incomparably low cost of living make Egypt among the most popular places in the MENA region for off-shoring medicine testing “pharmerging countries” [24]. Egypt has 41 universities and 94 health-related faculties and medical schools. There are 24 faculties of medicine with up to 34 departments in each faculty. There are more than 42,000 faculty members and 344,000 postgraduate students, 140,000 physicians, 18,200 dentists, 37,500 pharmacists, 176,000 nurses, and 35,000 physical therapists. Clinical research including clinical trials is an essential mandate for getting masters and doctorate degrees. Moreover, clinical research for publication is a mandate for promotion for faculty members according to the rules of the supreme council of Egyptian universities [23].

According to the Professional Ethics Regulations issued by the Ministry of Health (MOH) No. 238/2003, part four: “conducting medical research and experiments on human beings, any experiments for drugs and techniques on human beings prior to being endorsed by the competent quarters and acquiring a detailed study of the risks/benefits relationship are prohibited.” The volunteers must comply in a clear way of the targets of the research, the research approaches, the benefits expected, the probable risks, and the extent of their effect on them with official written consent and/or approval of the official guardian or curator in the presence of a prosecution witness. The volunteers have the right to cease or withdraw from the research without sustaining any negative consequences. The researcher is required to submit a detailed and clear research targets report with justifications for conducting it on human beings to the approving authority for approval [25]. The same meaning was maintained in Law 71/2009 and a new draft law of 2014 [26, 27]. However, this draft caused much public concern because it contained an article allowing trials on children, pregnant women, drug addicts, detainees, and psychiatric patients. According to critics, it would have paved the way to experimentation of medicines on vulnerable people. Thus, this law has never seen the light of day [27].

The researcher is expected to discontinue any experiments on human beings if the accompanying risks exceed the benefits expected of the research and ensuring all preventive, diagnostic, and therapeutic methods for each patient for conducting the study. The draft of the national law on clinical trials driven from the constitution of Egypt that was leaked to the media in 2014 tried to lift those safeguards [27].

Besides these regulations, more than 56 RECs and Institutional Review Board (IRB) registered were designed in many health-related faculties, foundations, and institutes in Alexandria, Assuit, Aswan, BeniSuif, Benha, Fayoum, Giza, Ismailia, Mansoura, Minia, Sohag, Tanta, and Zagazig. Egyptian Network of Research Ethics Committees (ENREC) was created in 2008 to raise the harmonization between Research Ethics Committees, facilitate more uniform ethical review, and simplify REC procedures and standards [6].

Since there is no robust legislative constraints and clear guidance to charge entities or stakeholders involved in overseeing or executing clinical trials, concerns are increasingly being raised, whether ethical pitfalls of clinical research are adequately addressed, and whether the safety and the rights of subjects are constantly prioritized and maintained, leaving room for

different interpretations and making it more difficult to identify violations and impose sanctions [28, 29]. Unlike other emerging countries, Egypt does not make it obligatory to have clinical trials conducted on their population before marketing approval is granted [30]. Moreover, there are concerns that RECs in Egypt may not be able to provide high standards of human subjects' protection due to its inadequate functioning ethics review system and reluctance of the national regulations and bureaucracy that occurs when they interact with the MOH [22, 31].

An extensive review carried out by multiorganizations, published in June 2016 and based on United Nation International Aid Program (UNIAID), Egyptian experts and clinical trial participants' interviewee and various media reports, many critics were assumed. Although they admit that the current requirements of Egypt's regulatory authorities that no clinical trial sponsored by a TNC can be conducted in Egypt unless the product being tested has been granted market approval in the originating country with several Egyptian experts interviewed during this research confirmed this prerequisite, they pointed to the absence of regulatory obligation to conduct clinical trials in the country before being able to request a license for the drug. This "conditional approval" may happen based on medical grounds such as genetic or disease specificities prevailing in Egypt [22].

Of the 57 international drug trials that were active in Egypt in February 2016, Declaration of Helsinki concluded that the vast majority are late-stage clinical trials related to products already licensed in high-income countries. However, 16% are Phase I and Phase II trials, raising ethical issues as to the relevance and benefit of these trials for the Egyptian population since tests on these medical products were completed elsewhere for marketing approval in a high-income country. These include cancer trials testing medicines that were not yet registered in high-income countries, off-label use, had no specific protection mechanism for vulnerable participants, and no posttrial treatment access mechanisms. International experts raised doubts about the scientific validity of the designs of several of these cancer trials [32].

- Kotb in 2012 recounts an incident that was under official investigation. The trials used drug ursofalk (ursodeoxycholic acid) that was conducted on children at one of Cairo University's hospitals, providing evidence that only 9% of the children improved while most of the cohort receiving treatment developed hepatic failure, lethal pneumonia, otitis media, and ascites with high incidence of death was uncovered [33].
- According to the Declaration of Helsinki Study, cancer trials described in Egypt were considered to be the clearest illustration of the vulnerability of trial participants and the profound inequality of their situation compared to cancer patients in wealthier nations. Due to the high prices of cancer treatments, experimental drugs may be the only medication that Egyptian cancer patient will receive. As such, they run an unknown risk of experiencing serious side effects while already suffering a serious disease [34].
- Egypt has the highest prevalence of viral hepatitis C in the world and was the first low- or middle-income country in 2014 to negotiate preferential pricing for the new direct acting antiviral (DAA) treatment sofosbuvir (Sovaldi) with manufacturer Gilead [35]. However, the deal (US\$ 300 per month of treatment instead of US\$ 84,000 in the U.S.) was criticized

for its opacity. The “Sovaldi deal” generated diverging opinions among Egyptian experts as to whether the state-subsidized free treatment program is, in fact, a disguised clinical trial of national scale [36]. Given the absence of patent protection, several Egyptian companies were able to produce generic versions of DAAs for the market [32].

Ethics in health research is a collective consciousness and concerns of researchers, institutes, funders, medical journals’ editors, regulatory agencies, and others. Ethical approval by one of these entities does not relieve others from responsibility. Egyptian authorities should develop a single, robust legislative framework with a functional independent control system that takes the DH and the Council for International Organizations of Medical Research (CIOMS) Guidelines as their reference point for ethical standards. Egyptian authorities should also create an online, regularly updated public registry of clinical trials conducted in Egypt. Ensuring access to information must be guaranteed, as it is a fundamental prerequisite to enable civil society to play its role in signaling, observing, auditing, and unveiling unethical clinical trials practices.

#### **2.4. Tanta Faculty of Medicine model experience**

University hospitals have their own in-house IRBs, which provide training to medical doctors and researchers participating in clinical trials. The only mechanism available to protect participants is the REC in the MOH, in the research centers, and in university hospitals [37].

To develop an educational and medical research policy in Tanta Faculty of Medicine, we plan the following standards to be on the track of international standards.

##### *2.4.1. Research Ethics Committee*

Research Ethics Committee (REC) plays a central role of ethical oversight of research involving humans or animals in our organization. REC reviews research proposals involving human or animal participants to ensure that they are ethically acceptable and in accordance with relevant standards and guidelines. Our REC includes institutional review board members and was organized and approved at the Faculty and University levels in June 2010.

In undertaking this role, REC is guided by relevant standards, which include those in the *International Statement on Ethical Conduct in Human Research* issued by CIOMS and WHO [38, 39]. Consequently, this Statement identifies the demands, principles, and values by which research should be designed and applied and to which HREC should refer when reviewing research proposals.

It also sets up requirements and responsibilities for:

- Researchers in submitting research proposals to REC.
- REC in:
  - (1) Considering and reaching decisions regarding these proposals and in monitoring the conduct of approved research plus to monitor and reporting any scientific misconduct.

- (2) Developing awareness and teaching the ethics of scientific research for the faculty post-graduate and undergraduate students.
- (3) Cooperation with the ethics committees of scientific research counterparts in Egypt, the Arab, and foreign countries.

#### 2.4.2. *Research plan*

In general, the educational mission of the Faculties of Medicine is fortified by a highly successful research enterprise that includes widely varied scientific fields such as basic molecular and cellular biology and population health as well as hospital and community applied clinical researches.

Our institution's goal was to develop a plan to support research excellence in strategic areas, train the next generation of health researchers, and facilitate the translation of new knowledge into beneficial health outcomes for the patients, the population, and policy makers. Our Faculty has developed and established a strategic research plan in 2010. This plan was reviewed and modified according to Tanta University research plan and updated the paths proposed by the Ministry of Higher Education, then reapproved in June 2015. These plans are the outcome of an institutional planning committee after extensive consultation with all faculty departments.

### 2.5. The settled research priorities and guidelines of the ongoing plan are

Nine health-related areas of high priority were chosen guided by the international standards and based on the approved research plan of our university, mission, and vision of our faculty, needs assessment of the community at local, national and regional levels, interests and specialties of our staff members, available research resources including that supplied by scientific and health organizations with mutual interest, and the updates in science and medicine [40].

These research priorities are:

- (1) Cancer research: to foster basic as well as clinical research in the field of early diagnosis, recent treatment modalities, and prevention.
- (2) Emerging national health problems: The epidemiology, health effects, prevention, and eradication of emerging national health problems, e.g., hepatitis, H1N1, parasitic, and endemic diseases in our country.
- (3) Organ transplantation and artificial prostheses.
- (4) Obesity researches: causes, treatment, and prevention.
- (5) Immunogenetic diseases: our vision is to implement research in biotechnology.

- (6) Geriatric diseases.
- (7) Regenerative medicine and stem cell therapy: Tanta Faculty of Medicine is catching up with the research in the area of tissue culture and application of the concept of stem therapy in medicine.
- (8) Minimal interventional medicine and surgery (MIS).
- (9) Emergency medicine.

Our REC has reviewed 2823 research protocols and project proposals in the last 6 years up to July 31, 2016. Note that 1705 proposals (60.4%) were accepted while 1118 (39.6%) needed modifications with rejection rate of 18% after corrections. The activity of REC has significant impact on our research. In 2011, Tanta Faculty of Medicine had about 140 international publication cited on PubMed, this number reached 616 at the beginning of 2016 with almost threefold increase in 5 years. Additionally, in an attempt to strengthen medical research, we established our official medical journal (Tanta Med J) as an online peer-reviewed journal published by Wolters Kluwer—Medknow. Since January 30, 2014, more than 200 articles were published in it apart from those cited in PubMed.

The REC committee has members from academic and clinical medical departments. They are selected based on their experience in different medical fields and their reputation for a term of 3 years. To insure its independence, our Faculty Dean and Vice deans were excluded from the committee board. The committee members also included representatives of the community: professor in Islamic religion, representative of the Orthodox Church, governor (or his representative), certified trainer in research ethics, certified trainer in human rights, and a judge as representative of the legal authority. Clear regulations were approved to support the committee's role. The number of the committee members range from 5 to 15 according to its regulations (in the current term there are 13 members), they meet on a monthly basis to discuss research proposals and to follow-up on approved projects. The committee pays members a very small incentive for each meeting and there are no fees charged for protocol review. IRBs face numerous obstacles to achieving their goals, as there is no law in Egypt that regulates the selection of members of IRBs. Other problems include budget constraints, inability to monitor approved protocols continuously, and a lack of national guidelines and accreditation mechanisms for IRBs. These points are our future concern to improve the performance of REC.

### **3. Background**

Poverty accounts for almost one-third of the global burden of disease and there is a definite relationship between wealth/poverty and health/disease, although this relationship is not linear [41]. In “developing” countries, where cultural, linguistic, economic, and other barriers

may prevail between researchers and subjects, it is especially important to ensure effective communication [42, 43].

The medical industry is not exempted from the development of globalization, and the number of medical research studies conducted in developing nations, instead of in Western countries, has rapidly increased to gain more financial and scientific benefits [44, 45].

### **3.1. Advantages of conducting medical research in developing countries**

When the United States' National Bioethics Advisory Commission (US-NBAC) asked a pharmaceutical researcher why the industry seeks to conduct studies in developing countries, the answer was that the pharmaceutical industry is not a charitable business. It is a profitable Wall Street hard-core business [46]. There are several reasons that attract these companies to conduct their research in developing countries. Ruth Macklin divides these reasons into financial and scientific [45].

From sponsors' point of view, the main financial reasons are that the speed of research is faster in the developing country due to less oversight, thereby enabling the company gain approval for marketing and realize a profit sooner [46]. Research can often be done faster in those areas as time-consuming legislative requirements and local ethical review committees are not as well established in developing countries as in Western countries. Macklin points out that financially it is cheaper to carry out research in developing countries as they can offer lower costs for all of the ancillary goods and services necessary to set up and support the research, including labor costs for technical and scientific personnel [47].

Lack of awareness among participants about the methods and reasoning of research in healthcare may lead to therapeutic misconception as participants believe that the main goal of research is to provide them with therapy not to obtain information. For this reason, the US-NBAC recommended that investigators working overseas must indicate in their research protocols how they intend to minimize the possibility of therapeutic fallacy [48, 49].

### **3.2. Excellence in medical research**

Regrettably, 50 years after the Nuremberg trials and the Nuremberg Code, unethical medical research on humans continues, even in highly privileged countries [50–52]. Similarly, the continuation of human and patient rights abuses for 50 years after the Universal Declaration of Human Rights, even in wealthy industrialized countries, illustrates how difficult it is to achieve such universal moral aspirations [53, 54]. How research be regulated to avoid the errors and indiscretions of the past and to avoid new forms of discrimination and victimization in the increasingly complex era of biotechnology?

Early in 1993, the Council for International Organizations of Medical Research (CIOMS) launched its guidelines endorsing that ethical values must reinforce respect for the dignity of research subjects and to minimize risk, maximize benefits, make convenient compensation for time, provide reparation for any damage occurring during the research, protect confidentiality, and avoid conflict of interest [55–60].

### **3.3. Methods to achieve universal standards**

Universal ethical standards are still a debatable complex issue, which requires reflection on some issues. First, the best interests of subjects that may differ significantly according to personal and cultural priority and the magnitude of achievement in any situation. Second, what is considered truly universal? Third, is the entity of contextual issues that could be considered moral without resorting to ethical relativism [61–64]. Among those, recognition and dealing with contextual differences is a must to avoid both ethical imperialism and ethical relativism [65, 66].

### **3.4. International ethical guidelines**

Different countries have different laws, different views on human rights, and different ethical principles. Most countries in the developed world have their own set of laws and regulations concerning research with human subjects. These laws and regulations emphasize the key principles of human research such as informed consent, risk minimization, reasonable risk-benefit ratio, and confidentiality [67].

Developing countries may not possess such regulations or if they do, the regulations are weaker. Additionally, there are no international laws on medical research that apply in all countries to which all researchers conducting studies in another country must follow. However, there are international ethical guidelines for conducting medical research that can be followed in order to design and conduct an ethical research in a developing country. The most widely accepted are the Nuremberg Code, the DH, and the guidelines developed by the CIOMS [67].

### **3.5. Research ethics committees in developing countries**

In many developing countries, ethics has been paid insufficient attention. There is minimal similarity in the organization of research ethics committees (RECs) and little if any public responsibility. Existence of self-appointed private RECs lacking in expertise and liability, the absence of rational discourse, and possibilities of undeclared conflict of interest express most problems in some countries [59, 60].

### **3.6. Comprehensive guidelines for research ethics in developing countries**

Many categories of issues require special consideration in formulating new guidelines for biomedical research on human subjects in “developing” countries. Incommensurable load of diseases aggravated by the extent of destitution and high levels of illiteracy is a major issue to be considered. Differences between patients’ categories lead to added rights and ethical consideration in special groups by age or disease. Imbalance between the needed and actual resources available for research and basic health care with wide differences in access to health care is another important category. Finally, inadequate scientific and ethics infrastructures for the required reviewing process are a key issue [68, 69].

## **4. Concept of medical research**

### **4.1. Value of medical research**

Research is explained by Health Insurance Portability and Accountability Act (HIPAA) including the Privacy Rule and the Common Rule as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalized knowledge” [70, 71].

Data analysis collected for either diagnostic or treatment purposes can be used for secondary research purposes. These purposes could be health services or public health research that include analysis of occurrences’ patterns, determinants, natural history of disease, drug safety surveillance, and some genetic and/or social studies [72–74].

### **4.2. The importance of medical research**

Medical research serves as sources of important information about disease outcomes, drift and risk factors, functional abilities, patterns of care, and health care costs. Clinical trials are sources of important notification about the efficacy and adverse effects of medical interventions by controlling the variables that could influence the study results [73, 74].

Food and Drug Administration (FDA) approval of a drug for a particular indication relies upon a series of controlled clinical trials. Guidelines for best practices with high-quality patient care can be achieved by recording and assessing experience in clinical practice [75]. Economists notice that medical research has a positive effect on human health and life span which in turn increase productivity that will be reflected on the national economy [76].

### **4.3. The globalization of medical research**

Medical research goes globalization is a familiar term. Globalization has brought on economic benefits such as higher production rates, more efficiency, industrialization, and faster growing knowledge and innovation for those countries that are a part of it. We hear about poor working environment and low salaries in developing countries, a situation that Western companies have taken advantage of, which makes us think that everything that follows is not always morally justifiable [77].

The pharmaceutical industry is not exempted from globalization and has embraced it as a core component of their business models, especially in the realm of clinical trials. Industry and government sponsors in wealthier countries move their research trials to less wealthy countries. The majority of medical research is currently sponsored and conducted by private pharmaceutical companies [78].

Medical research proved the fact that globalization of commerce, trade, industry, and travel means that diseases can spread easily across the globe. For example, HIV spread from Africa and around the world and each year a new strain of the influenza virus emerges in Southeast Asia and spreads throughout the globe. As diseases have become international, medical research should also become international [77].

#### 4.4. The value and importance of medical information privacy

Medical privacy and confidentiality are vital to improving human health and health care. Protecting patients involved in research from harm or abuse and preserving their rights is essential to ethical research. Privacy has a value at the societal level as it permits complex activities, including research and public health activities to be carried out in ways that protect individuals' dignity without violating their rights [79].

##### 4.4.1. Value of privacy

Privacy is simply used to designate different concepts as the right to body safety or to be free from supervision. All information being gathered, the intentions of the parties involved, as well as the politics and cultural probability [80, 81]. Privacy denotes those concerned with personal information collection, storage, and examine whether data can be collected either for primary or secondary purposes [82].

##### 4.4.2. The importance of privacy

There are a variety of reasons for placing a high value on protecting the privacy, confidentiality, and security of health information [83]. Some theorists believe that respecting privacy (and autonomy) is a form of recognition of the attributes that give humans their moral uniqueness and part of human rights [84, 85].

Privacy facilitates and promotes other *fundamental values*, including ideals of personhood [86, 87] such as:

- Personal autonomy (the ability to make personal decisions)
- Individuality
- Respect
- Dignity and worth as human beings

Perceptions of privacy vary among individuals and various groups. Data that are considered intensely private by one person may not be by others [74].

#### 4.5. Distinguish medical research from practice

Privacy rule can differentiate between medical research and similar health care practices as public health practice, quality improvement activities, and program evaluations [88] and writing reviews [76]. However, specifying which activities meet the definition of "research" is a major challenge for privacy boards [89]. Neither the regulations of investigators and health care practitioners nor their interpretations by HHS denote clear guidelines on how to distinguish research from activities that use similar techniques to analyze health information [90]. Unfortunately, failure to correctly denote an activity as research could potentially allow improper disclosure of personally identifiable health information without sufficient oversight [91].

#### 4.6. Genetic information and the privacy rule

Research involving genetic information presents perhaps some of the most challenging areas for protecting the privacy of health information [92–94]. Recently, development makes it possible to learn a great deal about disease processes and individual variations in treatment effectiveness or susceptibility to disease from genetic analyses as the DNA sequences comprising a person's genome strongly influence a person's health.

Human genome knowledge, combined with advances in computing capabilities, can help decipher the roles that genetics and the environment play in the origins of complex but common human diseases as cancer. Patient samples stored in bio-specimen banks can provide a wealth of information for addressing long-standing questions about health and disease, and efforts are underway to create large genomic databases for that purpose [74, 94]. These data are of paramount importance for any community that could affect the national security. Based on the strict privacy rules inside the European Union than the United States, DNA is not direct identifier in Europe [95].

Genetic information does not itself identify an individual in the absence of other identifying information. Person's genetic code could be interpreted as a unique identifier and used to match a sequence in another databank, which includes identifiers [96, 97].

The NIH starts requiring data from the Genome-Wide Association Study in January 2008. That database became publicly accessible until August 2008 then NIH removed the database from the public Website regarding patient privacy [95, 98]. Those concerns stemmed from a study showing that a new type of DNA analysis could confirm the identity of an individual in a pool of similarly masked data if that person's genetic profile was already known [99]. NIH intends to move the aggregate genotype data to a secure, controlled-access database with policies for review and approval of data access requests in very strict manner [98].

### 5. International ethical standards in medical research

#### 5.1. History and legal basis of research ethics

Research ethics is mostly developed as a concept in medical research, but the general principles apply for all fields of research. Informed consent and confidentiality are important for both sociological study and clinical research keeping both human and patient rights. As a reaction to malpractices that were revealed during the Nuremberg trials, the World Medical Association (established in Paris in 1947) adopted the DH in 1964, in Finland [100].

The DH stated that "for all research, the well-being of the individuals is the most important over all other interests and sets principles for medical research combined with medical care" [60].

#### 5.2. The Nuremberg Code

The Nuremberg Code was the first international code of ethics for research on human subjects, introduced in 1947 after WWII, when the Nazi's outrageous experiments on human

subjects were revealed to the world. The Nuremberg Code focused on medical research, consisting of only 10 rules which indicated the most basic and essential principles [101]. In fact, the Nuremberg Code has had a major influence on human rights law and medical ethics. In contrast, while the previous ethics codes focused on the obligations of the investigator toward the research subjects, the Nuremberg Code reverses that logic: The rights are directly awarded to the research subjects who is actually revoluted to the view on research ethics [102].

### **5.3. The Declaration of Helsinki (DH)**

The World Medical Association (WMA) introduced the DH in 1964 to provide additional guidance for researchers beyond what was included in the Nuremberg Code [103]. Hence, the Declaration is longer and more detailed (37 articles) than the Nuremberg Code (10 articles). Since the publication of the DH, it has been amended nine times, most recently in October 2013 [104]. The DH is considered the best-known and most widely available guideline in medical research ethics [104].

The DH covers a broad assortment of topics such as privacy and confidentiality, research oversight, protocol development, protection of vulnerable subjects, publication, scientific design, the use of placebos, and access to treatments [104]. In many countries, the HD has been enacted as law (such as the Nuremberg Code in some U.S. courts), and adherence to its principles is a requirement of many national and international guidelines [105].

### **5.4. International Ethical Guidance from the Council for International Organizations of Medical Sciences (CIOMS)**

The CIOMS was formally constituted by the WHO and the United Nations Educational, Scientific, and Cultural Organization (UNESCO) in 1949, and it still remains under the aegis of these two specialized UN agencies. In 1982, CIOMS proposed the International Ethical Guidelines for Biomedical Research Involving Human Subjects. The purpose of these guidelines was to indicate how the ethical principles that were set forth in the 1975 version of the DH could be effectively applied. Emphasis was on application in developing countries, given their socioeconomic circumstances, laws, regulations, and executive and administrative arrangements. The guidelines were revised in 1993 and in 2002 [106]. The CIOMS guidelines are more detailed than the DH. They consist of 21 articles with many commentaries for each article which explain in detail many different situations. The CIOMS guidelines have had covered the topics of ethical justification and scientific validity of research, ethical review committees, informed consent registration, susceptibility of individuals, risk/benefits relationship, choice of control in clinical trials, privacy, compensation for injury in research, and national capacity to provide healthcare services [107].

In the meanwhile, the agreement on Human Rights and Biomedicine or the Oviedo Convention, adopted by the Ministers of the Council of Europe in 1996, stated that there is a strong connection between research ethics and human rights [108–110]. Including the primacy of the interest and human well-being, informed consent, and privacy are the corners of the research. The agreement sets standards for the use of the human genome and human embryos research [111].

UNESCO's Universal Declaration on Bioethics and Human Rights and CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects are all other important international declarations and agreement [112, 113].

Within the European regulatory framework, research ethics is based on the evident European commitment to human rights. Firmly enshrined in the treaties, compliance with human rights is fundamental for all European policy domains [114].

### 5.5. Informed consent and conflict of obligations

Informed consent constitutes the cornerstone of research ethics in human subjects. It is the most important to recognize that there are differences between informed consent for participation in research and informed consent for patient care. Its importance is to unravel the gray zone especially in vulnerable groups [115, 116].

A great problem occurred when the doctor is both the investigator and the provider of patient care [115, 116], especially in developing countries where it may be impossible to separate the roles of investigator and care giver. In this case, the conflict of interest in many occasions could be obvious concerning that in developing countries grossly inadequate health care resources and the pressures to enroll research subjects may concentrate more on patients' best interests [117].

Informed consent is basic requirement in research involving human being, research, genetic material or biological samples, and data collection. The rights and interests of the research subjects are fully respected especially during children research [117, 118], vulnerable adults (elderly, prisoners, mentally deficient persons, comatose, severely injured patients, and psychiatric patients), and people with certain cultural, religious, or traditional backgrounds [118].

There are various requirements for a valid informed consent that must be fulfilled, such as the four requirements that Jennifer S. Hawking explains per her quotation: "*First*, only those potential subjects who pass the requirements for decision-making competence should be asked to give consent (when it is necessary to enroll incompetent subjects an appropriate surrogate must give consent). *Second*, there must be full disclosure of all the relevant information, *Third*, the subject or surrogate must understand the information, and *Fourth*, he or she must then consent freely or voluntarily" [119].

Shamoo and Resnik specify three challenges of acquiring informed consent in developing countries. *First*, there is the possible presence of linguistic barriers that might make it difficult to acquire effective consent. It can be necessary to use interpreters in order to converse with subjects in their native language and translations of consent documents, and other material such as brochures, questionnaires, and visual aid must be produced. Some words may not translate easily into different languages which may affect interpretation of the text presented to the subjects. Furthermore, some populations may have no written language, so use of a consent form or other such document can be problematic [77]. The *second* challenge is that there can be conceptual or cultural obstacles to effective consent. People from developing and unindustrialized countries may have little comprehension of Western concepts such as disease, cause and effect, genetics/DNA, virus, bacteria, and so on.

In order to assure that the requirement of full understanding is met, it is necessary to adapt the form and content of procedures for obtaining informed consent to the educational level of the potential subjects of research [78]. *Third* and last, many African nations consist of tribal governance. The leaders of the tribe may need to give permission before any member of the tribe can be recruited into a study and the members may not believe they have any right to decide by themselves whether to participate or not. They may not even comprehend the notion of individual decision [77].

Ethical relativists have used cultural differences, like lack of understanding of the concept “individual consent,” as a defense for departing from widely accepted ethical standards for informed consent. Furthermore, in developing countries, women are sometimes thought of as less than men and their husbands sometimes make all the decisions, even those that only affect their wife’s health and her enrolment in medical studies [78].

### **5.6. Animal research ethics**

In Europe, the Commission report estimates that over 12 million animals are used for experimental or other scientific purposes each year. The most common used animals for these purposes are rodents, rabbits, mice, and rats [120].

The European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes, adopted in 1986, is the first important document protecting the animals used in experiments [114]. This directive since its application in 1986 is meant to ensure the protection of animals used in experiments or for other scientific purposes and sets standards for control on the use of laboratory animals, housing and care of the animals, and for the training of the personnel involved in the animal testing [114]. Apart from setting standards, the directive aims at reducing the numbers of animals used for experiments, following the concept of the “Three R’s (replacement, reduction, and refinement).”

For the Ethics Review organized by the European Commission, the researcher should provide all the details of the species (and strains) used, justify why they are used, explain why the anticipated benefits of the research justify the use of animals, and why methods avoiding the use of animals cannot be used [114, 115]. National authorities are responsible for the implementation of the Directive on the Protection of Animals [114].

### **5.7. Twelve golden rules to ethical research conduct**

According to the 12 golden rules, each researcher must ensure that his/her research will fulfill the following criteria [114, 121]:

Respects the persons before, during, and after the research, follow the “Do no harm” principle, realize the rights of individuals to privacy, personal data protection and freedom of movement, informed consent for human being research, treat animals with respect following the three Rs: Replacement, Reduction, and Refinement when designing animal research, never misuse terrorists or military organizations, respect integrity of an individual and that any modification (genetic or technological) does not interfere with this principle, always respect environment biodiversity, and finally build on the understanding that any benefits are for the good of the society [122–124].

## 6. Conclusions

The need for new and better treatment options for medical research continues unabated. As long as that need persists, medical trials are likely to continue. Many medical researches are driven by economic or academic interests that may or may not reflect the needs of the host country.

The pharmaceutical industry is not a charitable business but it is a profitable one. There are many reasons that attract these companies, researchers, and sponsors to conduct their research in a developing country.

Many moral lessons have been learnt from the history of medical research. Regrettably, 50 years after the Nuremberg trials and the Nuremberg Code, unethical medical research on humans continues.

Protecting patients involved in research from harm or abuse and preserving their rights is essential to ethical research. Human rights, health development, and medical research ethics can be gathered together when standards are followed with minimizing bias and conflict of interests. Informed consent and confidentiality are important for both sociological study and clinical research keeping both human and patient rights.

Human and animal rights should be preserved in all categories of medical research. Quality of research in the medical field will be reflected on the quality of health care and welfare of the community whether it is performed in developing or developed countries. The 3 R's: Replacement, Reduction, and Refinement have to be followed. International guidelines provided by WHO, DH, CIOMS, WMA, UNESCO, and Nuremberg Code need to be ascertained in research whether performed in developed or developing countries. Most, but not all developing countries, have ethical review committees in the form of research institutes or other scientific panels. However, the reality is that these panels need to be independent and able to review clinical trials without prejudice.

We do not want a scientifically neat study if it is ethically flawed, we need to redouble our commitment to the highest ethical standards, no matter where the research is conducted, and sponsoring agencies need to enforce those standards.

The Tanta experience can be taken as a role model in developing countries to initiate guidelines to standardize the ethics of medical research at national and regional levels.

### Author details

Sherif M. Shehata<sup>1\*</sup>, Nehal M. ElMashad<sup>2</sup> and Azza M. Hassan<sup>3</sup>

\*Address all correspondence to: sherifshehata2001@yahoo.com

1 Department of Pediatric Surgery, Faculty of Medicine, Tanta University, Tanta, Egypt

2 Department of Medical Oncology, Faculty of Medicine, Tanta University, Tanta, Egypt

3 Department of Medical Microbiology, Faculty of Medicine, Tanta University, Tanta, Egypt

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