

Clinical Research, Ethics of Clinical Research in China

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Abstract

Clinical research is very different in China and in the U.S. There is a rigorous set of rules and regulations enforced by the Food and Drug Administration and the National Institutes of Health in the U.S, but there are no enforced rules and regulations imposed by the Chinese government in China. There are several formal educational systems that teach the fundamentals of rigorous clinical research in the U.S, but none in China. It is acknowledged that truth is essential for research in the U.S but not in China. There is an abundance of support for clinical research in the U.S but not in China. In this “think piece” clinical research is contrasted in the U.S and China.

Introduction

I am personally very interested in the interfaces between clinical research, the ethics of clinical research, and China since I have just completed a long career doing clinical research with new drugs, overseeing clinical research as Director of an academic (the Johns Hopkins University School of Medicine) Division of Clinical Pharmacology, regulating clinical research and the ethics of human experimentation as chair of an Institutional Review Board (IRB), and teaching about clinical research as a physician-scientist at a research oriented medical school and as a founder and teacher in the first Ph.D. degree granting program in clinical investigation in the United States, namely the Johns Hopkins Graduate Training Program in Clinical Investigation (GTPCI) [1]. In addition, for over 40 years I have been a faculty member of a medical school committed to helping my medical school become a global institution with a mission to help educate the future leaders of medicine (both in the United States and internationally) by creating relationships between our faculty and the faculty of various foreign institutions.

It was then somewhat surprising for me to realize that the juxtapositions of clinical research in the U.S. and China have only rarely been written about. This may be because clinical research has predominantly been developed as a result of drug development and, prior to the 20th century, there was very little formal and serious drug development (clinical research) anywhere in the world. This, in turn, may well have been because so few drugs then were both effective and acceptably safe. In fact, Oliver Wendell Holmes, Senior (1809-1894), a physician (and father of the American Associate Supreme Court Justice Oliver Wendell Holmes, Junior), toward the end of the 19th century is said to have declared, “If all the drugs were thrown into the ocean, it would be all the worse for the fishes and all the better for mankind” [2]. I believe that this was true at that time in both the United States and China and in the rest of the world as well.

Clinical research (and drug development) has grown in the last hundred years primarily in the United States and Europe. Clinical research has still not “gained traction” and prospered in China. In fact it is only recently that basic science has once again begun to emerge in China and clinical research is far behind. My beliefs are based on many personal trips to China in the past ten years during which I have visited the Peking Union Medical College Hospital and the Chinese Academy of Medical I Sciences, (Beijing) the Peking University Health Science Center (Beijing) the Shanghai Medical College of Fudan University and several of its affiliated hospitals, the Shanghai Jiao Tong University School of Medicine (Shanghai) the Sun Yat Sen University and several

of its affiliated hospitals (Guangzhou), and Jilin University’s Norman Bethune College of Medicine Jilin University (Changchun).

I began my venture with a strong belief that China has some inherent advantages and that there seemed to be no inherent reason that clinical research could not be done as well and more efficiently in China than in the United States. My thinking has matured from the romantic to the realistic over the last ten or so years and I now wish to share my thoughts in hopes of starting a healthy discussion from both Chinese and Americans clinical investigators as well as others.

On one of my trips to China, I found that a prominent Chinese philosopher, Fung Yu-Lan, had written a paper in 1922 entitled “Why China Has No Science --- An Interpretation of the History and Consequences of Chinese Philosophy”. This paper was delivered orally at a bi-weekly conference of the Philosophy Department of Columbia University and published in English 65 years later, (1987) in Professor Fung Yu-Lan’s book entitled “Selected Philosophical Writings of Fung Yu-Lan” published by the Foreign Languages Press in Beijing [3]. In this paper Professor Fung quotes the eminent American Philosopher, Professor John Dewey, who wrote “It may be questioned whether the most enlightening thing he (the visitor) can do for others who are interested in China is not to share with them his discovery that China can only be known in terms of itself, and older European history. Yet one must repeat that China is changing rapidly; and that it is as foolish to go on thinking of it only in terms of old dynastic China as it is to interpret it by pigeon-holing its facts in Western conceptions. China is another world politically and economically speaking, a large and persistent world, and a world bound no one knows where?”[4]. Professor Fung then goes on to develop his theory about his original question, which he says was at the beginning of his academic career. Professor Fung states “If we compare Chinese history with the history of Europe of a few centuries ago, say before the Renaissance, we find that, although they are of different kinds, they are nevertheless on the same level, But now China is still old

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while the Western countries are already new, What keeps China back. It's a natural question. "He goes on to say "What keeps China back is that she has no science. The effect of this fact is not only plain in the material side, but also in the spiritual side, of the present condition of Chinese life. China produced her philosophy at the same time with, or a little before, the height of Athenian culture. Why did she not produce science at the same time with, or even before, the beginning of modern Europe? This paper is an attempt to answer this question in terms of China herself." Professor Fung ends the introduction to his paper by stating "At the end of this paper I shall venture the conclusion that China has no science, because according to her own standard of value she does need any."

In the sixth and final section of his paper Professor Fung finishes by saying "In one word China has no science, because of all philosophies the Chinese is the most human and the most practical. While the philosophers of the West are proud of their clear thinking and scientific knowledge, the Chinese philosopher would say with Marcus Aurelius "Thanks, too, that in spite of my ardour for philosophy I did not fall into the hands of a professor, or sit poring over essays or syllogism or become engrossed in scientific speculations. Nothing is more disheartening than the weary round of spying, probing (as Pindar says) "the depth of the earth", guessing at the secrets of our neighbors' souls, instead of realizing that it is enough to keep solely to the god within, and to serve him with all honesty ---". Professor Fung ends his essay with an extraordinarily non-judgmental conclusion as follows: "--- the West emphasizes what we have, the East emphasizes what we are the question as to reconcile these two so that humanity may be happy both in body and in mind is at present difficult to answer. Anyway the Chinese conception of life may be mistaken, but the Chinese experience cannot be a failure. If afterwards mankind shall become wiser and wiser, and think that they need peace and happiness in their mind, they may turn their attention to and gain something from, the Chinese wisdom. If they shall not think so, the mind energy of the Chinese people of four thousand years will yet not have been spent in vain. The failure itself may warn our children to stop searching for something in the barren land of human mind. This is one of China's contributions to mankind." This paper was first "read" in 1922 at Columbia University when Professor Fung was a student there. It was first printed in 1991 and there was a second printing in 1999.

I believe that one might ask the same question today (2012) and I believe that the following may be quite relevant:

- 1.) China was quite isolated until the 1970's, neither focusing on exporting Chinese medicines (allopathic or herbal) to the rest of the world nor the importation of drugs from multinational pharmaceutical companies for the huge Chinese home market.
- 2.) The rapid changes of China towards globalization in the 21st century need a revision of China's approach towards the importation and exportation of both drugs and herbal medicines if China wishes to trade.
- 3.) China has yet to appreciate the pivotal role of clinical research in the process of drug or herbal medicine development. Even though, in the last few years, China has poured billions of yuan (remimbi) into the basic sciences, China has yet to recognize the need for and the value of a solid scientific foundation for clinical research. In this way China is much like the U.S. of thirty to fifty years ago when the U.S. government spent billions on basic biomedical research and relatively little on clinical research.
- 4.) As a consequence, China has yet to recognize the tremendous

importance of and need for its government providing at least a small number of physicians with the paid time away from an overwhelming load of patient care to devote to reading, thinking, planning, carrying out, analyzing, and publishing the results of clinical research.

- 5.) There are very few mentors who are educated in the ways of rigorous clinical research and who can teach the fundamentals of clinical research to others in China.
- 6.) There are no formal training programs in China that provide substantial training in clinical research. Hour-long, day-long or week-long courses in Good Clinical Practice (GCP), even if given by outstanding imported speakers from the US and/or Europe simply will not constitute "education" in clinical research. Just as it takes several years to train as a basic scientist (getting a PhD for example), it may take at least as long to train in clinical investigation).
- 7.) There is no strong infrastructure at any Chinese Medical Institution that could or would participate, with the government, in the conduct of or the rigorous regulation of clinical research.

I assume and I believe that the protection of the public from the unregulated or erratically regulated production and distribution of drugs, other therapeutics, herbal medicines, and foods clearly falls within the domain of a combination of law and ethics in China just as it does in the United States. Having made that assumption, I believe that the development and regulation of drugs (allopathic but not herbal) in the United States is an excellent example to illustrate the regulation of clinical research. Drug development is uniquely relevant since, based on my experience as chairman of an Institutional Review Board (IRB), I estimate that about 60% of the clinical research coming before our Institutional IRBs is related to drug development, the other 40% to non-drug development related clinical research.

Herbal medicine development is clearly relevant in both the US and China and its regulation (or lack thereof) is highly relevant to both countries. Herbal medicine development offers a special opportunity for Chinese clinical research since herbal medicine is so revered in China and since so little about it is proven to be either effective or acceptably safe by a rigorous scientific method.

I shall contrast drug development in the United States.

The guidelines and regulations for the development of drugs must be clearly written and rigorously enforced if the public is to be protected.

The U.S. Food and Drug Administration (FDA) was created by an act of the U.S. Congress in 1906 in order to protect the American public from the shoddy nature of the production of both food and drugs at that time [5]. At its creation the FDA initiated the requirement that strict standards be imposed on the manufacturing of drugs and that the labeling of drugs honestly inform the public, the practitioners, and the researchers exactly what is in every marketed container of the drug. Without this scrutiny the drug simply could not be approved by the FDA for marketing. The FDA also was charged with enforcing the guidelines and regulations and, for the last hundred years the U.S.FDA has done so very well.

The Chinese State Food and Drug Administration (SFDA) was adopted at the 7th Meeting of the Standing Committee of the Sixth National People's Congress on September 20, 1984 and revised at the 20th Meeting of the Standing Committee of the Ninth National People's Congress on February 28, 2001[6]. I was amazed to find that one can

read this document from the Chinese government in English and on the internet. I was even more amazed to receive a response within a week to a letter that I wrote to the SFDA (in English). While in the past, I have been a strong defender of the U.S. FDA, I have not received a reply to a letter that I wrote to the U.S. FDA (*in English*) about ten years ago. I cannot defend the U.S. FDA's efficiency. I hate to think what would happen if my letter had been in Chinese.

The consequences of either having no guidelines and regulations or of not rigorously enforcing existing guidelines and regulations can be seen in both the United States and China. In the US the consequences of not having these guidelines can best be illustrated by considering the regulation of herbal medicines. In the U.S. herbal medicines are mostly categorized as "Complementary and Alternative Medicines" or "Food Supplements" or "Dietary Supplements". This situation arose because the oversight and the regulatory authority of the FDA were taken away from the FDA by an act of Congress that is known as the Dietary Supplement Health and Education Act or "DSHEA" [7]. The consequences can also be seen in the US because herbal medicines are categorized as "complementary and alternative medicines" or "food additives" or "dietary supplements" rather than drugs, and are exempted from the guidelines and regulations that apply to drugs (as a result of powerful lobbying on behalf of the herbal medicine industry). As a result no one, not care giver or researcher or patient (or anyone else), can know for sure what is in the herbal medicine container or what is being purchased or administered. This has two further consequences. First, from an ethical standpoint, it may well be unethical for any care giver to advocate or prescribe something that cannot be counted upon to contain anything that is both of value to the patient and acceptably safe, even if the label claims to contain such. Secondly, from a scientific standpoint, there is no way that the observations seen with the use of any herbal product can be repeated (an essential requirement for the scientific method).

These same consequences will exist even if there are guidelines and regulations, if these guidelines and regulations are not rigorously, fairly, and consistently enforced. In China herbal medicines are covered by the same SFDA regulations as are drugs but there appears to be a major problem with the strict enforcement of the written regulations. This major problem was illustrated dramatically by the indictment, conviction, and execution of the former chief of the SFDA in July of 2007. This was claimed to "*mark a clean start for its approach to drug regulation*". In August of 2007 an editorial in the prestigious journal *Nature* states "*Since 1998 Chinese drug regulators have, in theory, adopted many of the rules that govern the US Food and Drug Administration (FDA) – the largest and, arguably, most thorough drug regulator in the world. But the Chinese outfit resembles the FDA more in form than in substance, — the SFDA doesn't have the internal checks and balances that the FDA has—or its level of transparency*" [8,9]. This seems to have been prophetic since in 2010 the deputy director of the SFDA was arrested and accused of graft and corruption.

The regulations of 1904 in the U.S. were outstanding in terms of what they required and the FDA has been outstanding in its impartial and rigorous enforcement of these guidelines and regulations.

Nevertheless another disaster in 1937 in the U.S. led to a revision of the Federal Food, Drug, and Cosmetic Act in 1938 charging the FDA for the first time with oversight of all new drug development in the U.S., at least as far as safety was concerned [5]. An American drug company tried to formulate a liquid form of sulfanilamide for use in children (who could not swallow the tablets easily) and ethylene glycol

was used as the excipient to dissolve the sulfa drug. Ethylene glycol was terribly toxic and over 100 persons (mostly children) died. This act then required proof of safety before release of the drug onto the market. It was and is clear that the public needs to be protected from drugs or that are unacceptably toxic. But what is unacceptable toxicity? It is a truism that all drugs (and probably all herbal medicines as well) are toxic in some dose to some people. The identification of an adverse event and the proof of its severity and causal relationship with a drug can be very complicated and difficult. This has been seen over and over again in the US with drugs that either cause severe toxicities only very rarely (such as chloramphenicol) or drugs that cause toxicity that is disproportionate to their benefit. Perhaps another unusually good example is the toxicity caused by herbal medicines containing aristolochic acids from *Aristolochia* or other plant species [10].

Yet another disaster, this time in Europe, took place between 1957 and 1961 when thalidomide was widely sold and widely used as a mild sedative [5]. In 1961 an unusual type of birth defect (called phocomelia) was clearly shown to be caused by the intake of thalidomide during the first trimester of pregnancy and thalidomide was removed from the market in the U.S. and Europe in 1961.

In what might be seen as an over-reaction to this last disaster, another revision was made in the Federal Food, Drug, and Cosmetics Act in 1962 [5]. This added several new regulations onto the act that extended the drug regulatory power of the FDA. This Harris Kefauver or Drug Efficacy Amendment added the following to the Federal Food, Drug, and Cosmetics Act. Now, for the first time, it was required that a drug be proven to be effective for some symptom or disease prior to its marketing. In addition the FDA was given more power to insure the safety of drugs prior to marketing, to only disclose accurate information about the side effects of drugs, to insure that drug advertising disclose accurate information about the side effects of their drugs,, and to stop generic drugs from being marketed as expensive drugs under new trade names and as new "breakthrough" medications. It is interesting to note that none of these revisions, each of which may be advantageous in itself, can assure anyone that a tragedy similar to the thalidomide tragedy cannot happen again. Nevertheless, this is an excellent example of a truism in regulatory affairs and that is that after a disaster, committees almost always feel that they must act. In order to show that they are doing what they were created to do, even though their action may not solve, minimize or even address the problem.

The addition of effectiveness was very important to the FDA and added a huge but important burden for the drug developers and also for the clinical investigators and the regulators. However, all of these requirements were designed to add protection for the American public. The drug developers could no longer market drugs that were of no value to a patient and they had to prove to the FDA that their drug could do what they claimed that it could do. On the other hand, an herbal medicine did not have to pass this test in order to be marketed and this allowed the producers of herbal medicines to circumvent the FDA regulations for drugs and, as a result, save both the money and the time necessary to prove effectiveness. An unintended consequence, however, was that herbal medicines can be marketed in the US without any proof of effectiveness for anything of value for any disease or symptom, just like in the latter part of the 19th century in the U.S. when there was no FDA and when "snake oil salesman roamed our country.

The importance of a requirement for proof of effectiveness in both drug development and herbal medicine development cannot be over-emphasized. Furthermore, this part of drug and herbal medicine

development is where the interface between clinical research and ethics and both China and the U.S. is best appreciated.

Excellent clinical research is pivotal for both drug and herbal medicine development. No amount of preclinical or basic research (chemistry, biology, biochemistry, molecular biology, genetics, genomics, proteomics, cell biology, basic pharmacology, physiology, animal model study, or animal toxicology) can ever suffice for approval for clinical sales or use without the ultimate demonstration of effectiveness (and acceptable safety) in humans. This is the pivotal nature of clinical research.

An absolute requirement for both clinical research and basic research is honesty. In the preface to a small booklet entitled "On Being a Scientist: A Guide to Responsible Conduct in Research", the third edition of which was published in 1959 by the highly respected National Academy of Sciences, National Academy of Engineering, and Institute of Medicine of the United States, the first paragraph of the Preface states "*The scientific enterprise is built on a foundation of trust. Society trusts that scientific research results are an honest and accurate reflection of the researcher's work. Researchers equally trust that their colleagues have gathered data carefully, have used appropriate analytical and statistical techniques, have reported their results accurately, and have treated the work of others with respect. When this trust is misplaced and the professional standards of science are violated, researchers are undermined. This would impact the relationship between science and society*" [11].

It would be wonderful if all scientists were absolutely honest with respect to their scientific activities. Nevertheless, it appears that it is not easy for all scientists to always be honest in their science. It appears that constant vigilance must be exerted by some oversight group (probably governmental) in both the U.S. and China and surely in the rest of the world as well in order to minimize dishonesty. In the U.S. this oversight ultimately rests with the U.S. Food and Drug Administration (for the sales and marketing of both drugs and medicinal products) and the National Institutes of Health (for research support) and in China with the State Food and Drug Administration. In the U.S. the FDA has a century of respected, rigorous, fair, and consistent oversight over the discoverers, manufacturers, distributors, investigators, and marketers of drugs. The record of the SFDA is both less long and less rigorous. This raises the question of whether or not the clinical research that is essential for drug development can exist and prosper without absolute honesty.

The Chinese Understanding of "Clinical Research"

I have asked faculty members at several Chinese medical institutions if their institution does any clinical research and uniformly I'm told that the specific institution does indeed do clinical research, I then ask what kind of clinical research and almost always I'm told about a study with a drug company (usually multinational) where the "investigator" at the Chinese medical institution simply enters his/her patients into a company designed protocol. This is a type of clinical research but the most elementary of types of clinical research. I suggest that in these cases the physician-investigators are merely "purveyors of warm bodies", receiving some sort of remuneration for each patient entered into the study but not being a party to the origin of the question being addressed, not participating in the design of the study, not carrying out any (or only a tiny fraction) of the work of actually performing the study, not participating in the analysis of the study, and not participating in the writing or publication of the study results.

If this is categorized as clinical research, then there are some advantages and some inherent problems: Advantages include: 1. The sponsoring company has spent the necessary time and money to write the protocol, saving the "investigator" from thinking or writing of the protocol for the study, 2. The company has thoroughly vetted the protocol so that it has the greatest likelihood of producing the results that the company wants, 3. The company usually provides the personnel to actually carry out the study, 4. The company probably will interface with the institution and the government who make and enforce the regulations, and 5. The company will probably wish to collect and store all of the data collected, retrieve it, analyze it, and either publish it or keep it from being published.

On the other hand there are almost always serious disadvantages for the "investigators" as "purveyors of warm bodies": 1. The research is almost always part of the sponsoring (pharmaceutical or device) company's search for a marketing advantage (profit) and almost never focused on addressing an important scientific question generated by the investigator, 2. The investigators have no real intellectual input in the study, 3. The investigators rarely formulate the questions to be asked, 4. The investigators are not free to ask their own questions, 5. The investigators seldom learn much from participation in the study, 6. The research rarely, if ever, allows comparison between two alternative approaches to therapy if alternative therapy involves another company's product and thus comparative studies of two similar products rarely occur.

Clinical Research Focused on Traditional Chinese Medicines (Especially Herbal Medicines) Could be and Should be a Unique Opportunity for Clinical Research in China. Rigorous Clinical Research is Desparately Needed also for Stem Cell Research and for Gene Therapy as Well as for Herbal Medicines

Clinical research has an important and even pivotal role to play in the realm of research in general and China could and should be a part of this.

There are, however, three fundamental principles that must underlay the rigorous clinical research of any herbal medicine stem cell research, or gene therapy as well as any Western drug [12].

1. The product to be studied must be standardized and regulated. This must be done for both ethical and scientific reasons. For ethical reasons it is imperative that anyone studying an herbal medicine know exactly what is in the product and that it is constant over time and constant between batches. If this is not certain, then one will always be able to say that your findings, either research or therapeutic, apply to the stuff that you studied but that it is not the same as the stuff that I studied or used. For scientific reasons it is imperative that the product be standardized so that the experiment can be reproduced, a requirement for the scientific method.
2. The product that is studied must be scientifically proven to be of benefit to some condition that is of concern to the patient.
3. The product that is studied must be scientifically proven to be acceptably safe for the condition being treated.

My Observations

The evolution of clinical research in the United States can, perhaps, best be followed by observing its stature over the past 30 or so years in

the evolution of the NIH since the NIH sets the tone for the kind of research that is funded by the government in the United States.

While clinical research, especially as related to drug development, has flourished in the United States since the creation of the United States FDA one hundred years ago, it has been primarily considered to be the province of the pharmaceutical industry and therefore their obligation to support. From the early 1900's until the 1990's this situation led to a lack of stature for clinical research as contrasted with basic research and a very skewed funding towards basic research and away from clinical research by the U.S. National Institutes of Health. In fact the NIH supported some Clinical Research Centers, which supported some investigator-initiated clinical research but which viewed industry supported clinical research in a negative light. Then in early 1995 NIH Director Harold E. Varmus and his senior staff launched several initiatives to assess the status of clinical research in the United States [13]. He established the NIH Director's Panel on Clinical Research to be chaired by Dr. David G. Nathans of Harvard Medical School () and he asked Dr. Lawrence Shulman of the NIH to serve as an emissary for clinical research to the academic health centers to learn the views of those engaged in and responsible for clinical research and research training [14]. In 2004, the new Director of the NIH, Elias A. Zerhouni, produced a "roadmap" to identify major opportunities and gaps in biomedical research that the NIH as a whole must address to optimize its entire research portfolio and make the biggest impact on the progress of medical research [15]. This process, called the NIH Roadmap, outlined a vision for a more efficient and productive system of medical research and identifies the most compelling opportunities in three main areas: New Pathways to Discovery, Research Teams of the Future, and Re-engineering the Clinical Research Enterprise. These areas will provide the science, management, and personnel,

respectively, to help the NIH catalyze the changes needed to transform new scientific knowledge into tangible benefits for people. With these changes has come a remarkable positive change in the attitudes of the NIH and academia towards clinical research.

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