LECTURE

A brief introduction to institutional review boards in the United States

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ABSTRACT
China has become one of the main fields for international drug and device trials in the last twenty years. Although China has greatly strengthened the protection of human research participants over this time, there is still room for improvement. In order for Chinese investigators to participate in international clinical trials, compliance with internationally recognized ethical regulations is essential. In the United States (U.S.), research involving human subjects is reviewed by an ethics committee called the Institutional Review Board (IRB). In this article, we briefly introduce the background, composition, and function of the IRB in the U.S. to our Chinese investigators.

GLOBALIZATION OF CLINICAL RESEARCH AND ETHICAL CONCERNS

Economic globalization is an important development in the last twenty years. The globalization of clinical research is also an increasing phenomenon in the last decade, with many industry and government sponsors in developed countries choosing to conduct clinical trials in developing countries.[1] The percentage of active U.S. Food and Drug Administration (FDA) regulated research investigators, which are based outside the U.S., has grown from 22% to 43% between 2000 and 2014.[2] Data from the clinicaltrials.gov registry shows that only 36% of the registered studies are being conducted solely in the U.S., and a majority of the studies (162 768 of 254 325) are recruiting patients outside the U.S. in 2017.[3] Many clinical trials are being conducted in developing countries including countries in Eastern Europe, Asia, and South America.

China is one of the countries that attracts many U.S. pharmaceutical and device companies, due to its large pool of potential research participants, its overall lower cost of conducting research, and the existence of fewer regulatory barriers.[4, 5] In 2017, 10 132 studies registered at clinicaltrials.gov were recruiting subjects in China, accounting for 7% of all studies listed on this website.[3] The number of international clinical trials conducted in China will most likely continue to grow in the future.

Studies conducted outside the U.S., under an investigational new drug (IND) or investigational device exemption (IDE) application, must meet the same FDA regulatory requirements (21 CFR Part 312 or 21 CFR Part 812),[6,7] as if they were being conducted within the U.S.. Under 21 CFR 312.120(c)(1), and 21 CFR 814.15(a) and (b),[7] FDA will accept the results of a foreign clinical study not conducted under an IND or IDE, only if the study conforms to ethical principles contained in the Declaration of Helsinki or with the laws and regulations of the country in which the study is conducted, whichever provides greater protection of human subjects.[7,8]

There are clear advantages to conduct clinical research in developing countries for international pharmaceutical or device sponsors. At the same time, the globalization of clinical trials raises scientific and ethical concerns.[9,10] One major concern is the ethical oversight of research involving human subjects in developing countries. One survey study concluded that only 56% of the 670 researchers surveyed in developing countries reported that their research had been reviewed by a local ethical review committee or health ministry.[11]

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The ability to maintain a dynamic balance between participation in international clinical studies and compliance with internationally standardized ethical regulations and norms is a major concern to both study sponsors and to local site participants. China has made steady progress to strengthen the protection of human research participants in the last thirty years. More than 10 provinces and provincial level municipalities including Beijing, Shanghai and Guangzhou have established medical ethics committees, and almost all tertiary hospitals in Beijing had formed research ethics committees by 2016.[12] The Measure for the Ethical Review of Biomedical Research Involving Humans released in 2016 by the Chinese National Health and Family Planning Commission demands that medical and health institutions that do not have a research ethics committee may not conduct biomedical research involving human research participants.[12]

Although the system of life science ethics management is steadily taking shape, China has not established an ethics committee at the national level, and ethics review committees at the institutional level are insufficient in number across the country.[12] With increasing opportunities to take part in international clinical studies, there is a great need to establish both a national ethics committee and institutional level ethics review committees in China. In addition, ethics education that focuses on human subject protection and ethical compliance is also needed.

Developed countries in North America and Western Europe have been engaged in clinical studies for an extended period, and have established mature research administration structures for medical ethics. Since a great number of U.S pharmaceutical and device company sponsored clinical trials are being conducted in China, it is necessary for Chinese investigators and ethics committees to become familiar with the U.S regulations for protecting human subjects. In the following paragraphs, we will provide an overview on Institutional Review Boards (IRB) in the U.S.

BACKGROUND OF IRB

Unethical research has been conducted by many investigators and in many countries, including the United States. The Nuremberg Trials were conducted at the end of World War II to bring justice to Nazi leaders and physicians who had committed crimes against humanity in their treatment of the concentration camp internees. As part of the trial proceedings, the prosecution issued the Nuremberg Code, which laid out ethical standards and helped to form the foundation for the U.S. Federal Regulations. The core elements of the Nuremberg Code are the requirements for "voluntary and informed consent, a favorable risk/benefit analysis, and the right to withdraw from a study without penalty".[13]

In 1964, the World Medical Association met in Helsinki, Finland, and drafted the Declaration of Helsinki,[14] further outlining principles that had international impact for medical research involving human subjects. Since its inception, the Declaration of Helsinki has been amended seven times, the most recent revision taking place in 2013.[15] The current Declaration consists of 37 statements covering ethical principles for medical research involving human subjects. IRB Members are encouraged to become familiar with the Declaration of Helsinki and to apply the stated principles when making IRB determinations.

The U.S. conducted several unethical research studies, which eventually led to the formulation and implementation of policy and regulations to protect human participants. The infamous Tuskegee syphilis study, funded by the U.S. Public Health Service, was conducted between 1932 and 1972 at Tuskegee Institute to evaluate the natural history of untreated syphilis in African-American males.[16] The study was conducted for forty years without ethical review and it denied participants the effective treatment for this curable disease. This study became a milestone in the history of U.S. research regulations and was the main reason that the principle of justice was developed in the Belmont Report.

In 1974, the U.S Congress passed the National Research Act[17] in response to public reaction to the Tuskegee study. This Act established the modern IRB system for regulating research involving human subjects, and also formed the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research. The commission identified basic ethical principles for human subject research and developed guidelines to ensure that research is conducted in accordance with these principles.

In 1978, the National Commission issued the Belmont Report,[18] which outlined three fundamental ethical principles: respect for persons, beneficence, and justice. The principle of respect for persons includes two main ethical beliefs associated with individual autonomy: treat individuals as autonomous agents and protect persons with diminished autonomy. The principle of beneficence is viewed as an obligation to protect the well-being of the research subject, or in other words, this principle can be explained as "do unto others as you would have them do unto you". In the Belmont Report, the principle of justice is explained as "the potential risks of research should be borne equally by the members of our society that are likely to benefit from it".

With the Belmont Report as the foundation, the U.S Department of Health and Human Services (DHHS) and the FDA revised their existing human subject regulations in 1981. In 1991, the U.S. Federal Policy for Protection of Human Subjects or the "Common Rule" was published by the DHHS.[19] It is a set of Federal regulations for the ethical conduct of human subjects research. The Common

Rule has been adopted by seventeen separate U.S. Federal departments and agencies. The regulations, as set forth by DHHS in Title 45 Code of Federal Regulations Part 46 (45CFR46), provide the rules which ensure that ethical principles are followed.[20] 45CFR46 includes four subparts: Subpart A, also frequently referred to as "Common Rule", is the basic DHHS Policy for Protection of Human Research Subjects and includes all of the requirements for the function of IRBs; Subpart B is associated with additional protections for pregnant women, human fetuses, and neonates; Subpart C is related to additional protections for prisoners; and Subpart D provides additional protections for children. [Note: The Common Rule has recently been updated and was published in the Federal Register on January 19, 2017. It implements new steps to better protect human subjects involved in research. The new rules are due to go into effect in January 2018].

The U.S. Policy requires that any research involving human subjects that receives federal funding be approved by an Institutional Review Board. Many IRBs have voluntarily decided to apply the policy to all research, including both funded and unfunded studies. In addition, researchers at healthcare facilities or universities are also required to obtain IRB approval before they can conduct any research activities in their facilities. To ensure that the research data is being collected with the approval of an IRB, the majority of the scientific journals require evidence of IRB approval before a manuscript is accepted for publication.[21,22]

PURPOSE AND FUNCTION OF THE IRB

As stated by the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research in its report on IRBs, the primary purpose of the IRB is to provide independent review of research proposals to determine whether they meet ethical standards. The primary function of the IRB is to assure that the rights and welfare of human subjects are protected before, during, and after their participation in clinical studies through conducting initial protocol review, ongoing review, and monitoring adverse events. In this context, "research" is defined as a systematic investigation designed to develop or contribute to generalizable knowledge; "human subjects" are living individuals about whom the investigator obtains data through 1) intervention or interaction with the individual, or 2) obtains identifiable private information.[23] Other functions of IRB include ethics consultation, education, and monitoring of clinical studies. Furthermore, the IRB has the authority to sanction and enforce rules regarding noncompliant investigators by rejecting a proposal or terminating an investigation.[24]

For a research proposal to be ethically acceptable and comply with regulatory requirements, the IRB ascertains that risks to human subjects are minimized and reasonable in association to the importance of the knowledge the study is anticipated to produce, that the process of subject selection is fair, and that the consenting process is adequately conducted. In this context, "risk" is defined as the probability and magnitude of harm or injury occurring as a result of participation in a research study.

Federal regulations do not require the IRB to review the scientific validity of the study design; rather the rigorous review of the science is usually left to the funding agency's peer review process. When research is not funded, the scientific review may be provided by a review at a local level, e.g. department or division of an institution.[25]

COMPOSITION OF THE IRB

The U.S. Federal policy requires that an IRB have at least 5 members of varying backgrounds including a chair person, a scientific member, a non-scientific member, a representative of the community not affiliated with the institution, and a member of the institution. Potential members could include nurses, physicians, pharmacists, ethicists, attorneys, clergy, and community advocates.[24] No IRB may consist entirely of members of one profession, or of one gender. No IRB member may take part in the review of any project in which he or she has a conflicting interest, except to provide information requested by the IRB.

Per Federal regulations, the "IRB members must be sufficiently qualified through diverse experience and expertise to safeguard subjects' rights and welfare and to evaluate research acceptability related to laws, regulations, institutional commitments, and professional standards."[24] The diversity of members' backgrounds is important for taking into consideration their advice and counsel in safeguarding the rights and welfare of human subjects. The constitution of the board must provide the professional expertise necessary to review study activities and be able to decide the acceptability of the proposed research in respect to applicable law, regulations, and institutional standards of professional practice.

Ad hoc experts may be added to the board as needed, to ensure adequate protection for special groups of vulnerable subjects. 45CFR46 defines children, prisoners, pregnant women, human fetuses and neonates as vulnerable subjects. In addition, handicapped or mentally disabled persons are also considered vulnerable populations requiring special protection. The IRB needs to consider the inclusion of one or more members who are knowledgeable about and experienced in working with these groups of subjects. The Federal regulations also specify that an IRB may invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that of the IRB members, although these individuals may not vote with the IRB.

The membership list of the IRB must include name, education degrees, profession, role on the IRB, gender, and relationship with the institution. This document must be submitted to the Office for Human Research Protections (OHRP) and also be maintained in IRB records.

TYPES OF IRB

The IRB can be local (institutional or private), central or commercial. Most research proposals are submitted to a local IRB for review and approval. Some multisite trials may be submitted to a central IRB for review. A central IRB may serve as the single IRB of record for all clinical trial sites in a multi-center trial such as the National Cancer Institutes' Central IRB and the American Academy of Family Physicians National Research Network IRB. Use of a central IRB for multisite trials can improve the quality and efficiency of multi-center clinical trials. Both the U.S. FDA and the Office of Human Research Protections (OHRP) have encouraged the use of central IRBs for multi-center trials. The commercial IRB is a free standing IRB, which is not affiliated with an institution. The commercial IRB concept arose from a need to relieve the burden on smaller institutional review boards, a burden that has resulted from the increasing volume and the increasing complexity of protocols.[24]

LEVELS OF IRB REVIEW

There are three levels of IRB review established by the U.S. Federal regulation: exempt, expedited, and full committee review.[23,24] The review level determines the degree of oversight the IRB requires over the course of the project. Individual investigators do not have the authority to make determinations about the review level of their own studies. The level of review is determined solely by the IRB.

Exception from IRB review (Exempt Research)

Each institution is required to have a clear policy on who has the authority to determine what research is exempt under Federal regulations, and those who have authority to make this decision are expected to be well-acquainted with the interpretation and applicability of the regulations. [20] For example, a study using existing data that is publicly available or is recorded in a manner in which the subjects cannot be identified, either directly or indirectly, may be exempt from Federal regulations and does not require IRB review.

Expedited review

According to U.S. Federal Policy, in order to qualify for expedited review, the research activities must involve no more than minimal risk or be a minor change in previously approved research during the period for which approval was granted. The IRB chair or experienced reviewer(s), who are authorized by the chair, can review the research and approve it, or refer it to the IRB for a full board discussion (CFR46.101 (b)). "Minimal risk" is defined as "the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests".[20] Categories of research that may be qualified for expedited review are listed in federal website at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2013-may-20-letter-attachment-a/index.html. An example of a study that could meet expedited review criteria would be obtaining identifiable data by conducting a retrospective review of medical records.

Full Board (Committee) review

Research proposals that do not meet exempt or expedited review criteria require Full Board Review, also called Full Committee review. These are the studies that have more than minimal risk(s) to the subject. The proposals are reviewed and discussed at a convened meeting of IRB members, and a majority of the IRB members present must approve the proposal. If the board disapproves the proposal, the notification to the investigator must include the reason for the decision.[20]

CRITERIA FOR IRB APPROVAL OF RESEARCH

In order to approve a research proposal covered by the U.S. Federal policy, the IRB must determine if all of the requirements, outlined below, are satisfied (45CFR46.111).[20]

First, the risks of subjects are minimized by using sound research design and, when appropriate, using standard procedures already being performed on the subjects for diagnostic or treatment purposes. The proposal should demonstrate that the risks to subject are reasonable in relation to anticipated benefits, and the importance of the knowledge that may reasonably be expected to result. When evaluating risks and benefits, the IRB should only consider those risks and benefits that may result from the research, rather than long-range effects of applying knowledge gained in the research.

Second, the selection of subjects should be equitable. When evaluating the equitability, the IRB should consider the purposes of the research and the setting in which the research will be conducted. If a proposal involves vulnerable populations, the protocol should explain in detail how these subject protections will be maintained.

Third, unless informed consent requirement is waived, informed consent is required to be sought from each subject or the legally authorized representative. In

addition, the informed consent needs to be appropriately documented.

Fourth, the proposal should have a plan for monitoring research data to ensure data confidentiality and the safety of subject.

Fifth, the proposal should set up measures to protect the privacy of subject.

Sixth, if the proposal involves subjects who are likely to be vulnerable to coercion or undue influence, additional safeguards have to be included in the study proposal to protect the rights and welfare of these subjects. Vulnerable subjects include children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

The Full Committee of the IRB has the authority to approve or disapprove a proposal. The Full Committee can also suspend or terminate the approval of research that is not being conducted in accordance with the IRB's requirements or if the study procedures have been related with unexpected serious harm to subjects (45CFR46.113).[20]

IRB approval is not a one-time event; rather it is an ongoing process. The IRB conducts a thorough review of ongoing research at an interval appropriate to the degree of risk, but at least once per year.[20,24]

ADDITIONAL PROTECTION FOR CHILDREN INVOLVED AS SUBJECTS IN RESEARCH

Children as a vulnerable population with diminished autonomy and entitled for additional protection from undue influence and coercion. When a study involves children, IRB must take into consideration the special regulatory requirements that provide additional protection for children. Generally the U.S law consider any person under 18 years old to be a child. For any research involving children, the IRB needs to determine which of the four categories of research apply to the study:[26] (1). Research not involving greater than minimal risk to the children (45CFR46.404); (2). Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research. (45CFR46.405) (3). Research involving greater than minimal risk and no prospect of direct benefit to the individual child subjects involved in the research, but likely to yield generalizable knowledge about the subject's disorder or condition(45CFR46.406) (4). Research that the IRB believes does not meet the conditions of 45CFR46.404, 46.405, or 46.406, but finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children. U.S. Department of Health & Human Services regulations at 45CFR46 Subpart D permit IRB to approve the first three categories of research involving children as subjects.[20] The fourth category requires a special level of HHS review beyond that provided by the IRB.

Parents/legal guardians are expected to act in the best interests of their children and are trusted with the responsibility of providing permission or consent for enrolling their children in research studies. When research involving minimal risk or that providing prospect of benefit to an individual child requires consent from one parent/legal guardian, while all other categories of research requires permission from both parents/legal guardians. In addition to obtaining parental permission, researchers must obtain the child's assent, which has been considered as affirmative agreement to participate in research. In U.S., assent should be obtained from children aged 7−17 years. [26]

SUMMARY

Human subjects are a valuable resource for research and their safety must be protected. IRBs play a very important role in protecting human subjects from possible harm and exploitation. Independent IRB review ensures that ethical principles are followed and adequate and appropriate safeguards are in place to protect human subjects' rights and welfare, while they contribute to ethically and scientifically rigorous research.

Although China has made remarkable progress to strengthen the protection of human research participants, lack of national and institutional level ethics review boards is still a major barrier preventing more Chinese investigators from participation in international trials. We anticipate the situation will be changed dramatically in the next decade.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

REFERENCES

1. Thiers FA SA, Berdt ER. Trends in the globalization of clinical trials. *Nat Rev Drug Discov.* 2008;7:13-14.
2. K A. FDA Perspective on international clinical trials. In: Health USFaDA-PP, ed2014.
3. ClinicaTrials.gov. 2017; https://clinicaltrials.gov/ct2/resources/trends. Accessed September 13, 2017.
4. Bailey W CC, Sharma N. Make your move: Taking clinical trials to the best location. https://www.atkearney.com/health/article?/a/make-your-move-taking-clinical-trials-to-the-best-location. Accessed September 12, 2017.
5. Richar Chin MB. *Global Clinical Trials-Effective Implementation and Management. Elsevier Inc*.; 2011.

6.CFR-Code of Federal regulations Title 21. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=312. Accessed September 12, 2017.
7.CFR-Code of Federal Regulations Title 21.812. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=812. Accessed September 12, 2017.
8.Human subject protection; Foreign clinical studies not conducted under investigator new drug application; final rule. https://www.regulations.gov/document?D=FDA-2004-N-0061-0002&oldLink=false. Accessed September 2017, 2017.
9.Glickman SW, McHutchison JG, Peterson ED, et al. Ethical and scientific implications of the globalization of clinical research. *N Engl J Med.*2009;360:816-823.
10.Stough WG ZF, Pitt B, et al. Globalization of cardiovascular clinical research: the balance between meeting medical needs and maintaining scientific standards. *Am Heart J.* 2007;154:232-238.
11.Hyder AA WS, Khan AN, Teoh NB, Kass NE, Dawson L. Ethical review of research: a perspective from developing country researchers. *J Med Ethics.* 2004;30:68-72.
12.Zhang X ZW, Zhao Y. The chinese ethical review system and its compliance mechanisms. *TRUST-Equitable resarch partnerships.* 2016.
13.Nuremberg code. https://history.nih.gov/research/downloads/nuremberg.pdf. Accessed September 12, 2017.
14.Association WM. Deklaration von Helsinki. 1964; https://aix-scientifics.com/en/_helsinki64.html.
15.Declaraion of Helsinki. *JAMA*. 2013;310:2191.
16.CDC. U.S. public health service syphilis study at Tuskegee. https://www.cdc.gov/tuskegee/timeline.htm. Accessed September 12, 2017.
17.National Research Act. 1974; https://history.nih.gov/research/downloads/PL93-348.pdf. Accessed September 12, 2017.
18.Research TNCftPoHSoBaB. The Belmont Report. 1978; https://videocast.nih.gov/pdf/ohrp_belmont_report.pdf. Accessed September 20, 2017.
19.Federal policy for the protection of human subjects. https://www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/index.html. Accessed September 12, 2017.
20.Services USDoHH. Code of Federal Regulations Title 45 Public welfare part 46 protection of human subjects. https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html. Accessed September 13, 2017.
21.Graf C DL, Docking M, Jones J, Joshua S, McKerahan T, Ottmar M, Stevens A, Wates E, Wyatt D. Best practice guidelines on publishing ethics:a publisher's perspective, 2nd edition. *Int J Clin Pract.* 2014;68:1410-1428.
22.Lambton J. IRB approval is required for publication: Mortal lessons. *Clinical simulation in nursing.* 2011;7:e69-e70.
23.Protections. USDoHaHSOfHR. Institutional Review Board Guidebook. 1993; https://archive.hhs.gov/ohrp/irb/irb_preface.htm#a3.
24.Amdur R BA. Institutional review board-Member handbook. Third edition ed. Sudbury, Massachusetts: Jones and Bartlett Publishers; 2011.
25.Federman D HK, Lyman Rodriguez L. Responsible Research: A systems approach to protecting research participants. Washington, DC: National Academies Press; 2002.
26.Protections OoHr. Special protections for children as research subjects. 2016; https://www.hhs.gov/ohrp/regulations-and-policy/guidance/special-protections-for-children/index.html. Accessed December 15, 2017.

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