

Informed Consent and Ethical Review in Chinese Human Experimentation: Reflections on the “Golden Rice Event”

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HUMAN EXPERIMENTATION (such as in regard to pharmaceutical efficacy, medical equipment, medical technology, and medical methods) aims to promote the continuous development and application of medical technology so as to improve the human condition.¹ Human experimentation involves the interplay of rights and obligations among the sponsor, researcher, and research subjects. In this context, the *sponsor* is the person or organization that initiates, funds, and supervises the human trials, assuming corresponding responsibilities; the *researcher* is the physician or scientist who conducts the medical tests; and *research subjects* are the natural persons who participate in the trials.

With the continuous improvement of medical technology in China in recent years, legal issues connected with human experimentation have become increasingly prominent. In August 2012, the *American Journal of Clinical Nutrition* published a paper titled “ β -Carotene in Golden Rice is as good as β -carotene in oil at providing vitamin A to children.” The paper detailed that research groups from Tufts University, the Chinese Center for Disease Control and Prevention, and other scientific research institutions selected 72 healthy 6–8 year-old children in Hunan, China; divided them into three groups; and provided 24 children with 60 g of Golden Rice for 21 days while drawing their blood to measure the vitamin A concentrations. The results showed that the effect of the Golden Rice was as good as that of vitamin A capsules.² This experiment, known as the “Golden Rice event,” aroused strong feelings and led to vigorous discussion in China. This paper discusses the operation of (and problems with) China’s current legal system in regard to human experimentation in the context of this event.

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I. BASIC PREMISE OF HUMAN EXPERIMENTATION: INFORMED CONSENT OF SUBJECTS

The key issue in human experimentation, and the guarantor of the fundamental rights possessed by experimental subjects, is *informed consent*. This term refers to the process by which subjects voluntarily confirm their consent to participate in a clinical trial after being informed of all aspects of the trial. A signed and dated printed form is required as the documentary proof of this election to participate.³ The informed consent form provides documentary proof of each subject’s voluntary choice to participate in the trial.

The “Law of the People’s Republic of China on Medical Practitioners” (1998) requires that the physicians conducting a trial be approved to participate in human trials by the relevant hospital and also that they will obtain patients’ consent when implementing the experimental care (Paragraph 2 in Article 26). Subsequently, the China Food and Drug Administration (CFDA) and the Ministry of Health developed the “Good Clinical Practice” (enacted in 1999; revised in 2003), “Provisions for Medical Device Clinical Trials” (enacted in 2003), “Ethical Review Methods for Biomedical Research Involving Humans” (enacted in 2007), “Good Clinical Practice” (enacted in 2008), “Guiding Principles for Ethical Review of Drug Clinical Trials” (enacted in 2010), and other documents, all of which emphasize that the medical researchers *must* comply with the ethical principles established in the Declaration of Helsinki and require the obtaining of

¹D.Q. Huang, HEALTH: LAW AND LIFE ETHICS (Beijing: Law Press, 2004, at 235).

²Golden rice is a genetically modified rice that can, as a result of the changes, increase the amount of vitamin A in the body of one who eats it.

³See “The Drug Clinical Trial Ethics Review Guidelines,” published by the China Food and Drug Administration, 2010.

the subjects' informed consent. For informed consent to be meaningful and valid, subjects must be fully informed of the experimental risks, as well as the goals and methods of a clinical trial.

In medical experiments, researchers seek to verify whether a hypothesis or proposed method (or device or substance) can solve certain problems. The methods or means being researched will not have been fully proved to be safe for and effective in humans. In the research design, researchers must take the possible risks into account and do everything possible to reduce those risks; however, inasmuch as some risks will be unknown or inherent at the start of a trial, a certain amount of risk is inevitable or irreducible. In addition, it may be the case that the experiments are being conducted not necessarily to benefit the subjects themselves, but rather to treat or benefit other persons. Because subjects necessarily assume certain risks in the research, their informed consent becomes even more critical when the subjects are not the intended beneficiaries of the research.

Informed consent must include three elements: information, understanding, and voluntariness. The researchers must provide the subjects with complete information as it is known at the start of the trial, and the subjects must understand the information and have both the ability to give their consent and the opportunity to elect freely whether to participate in the research.⁴

A. Full Information

Full information means that the researchers provide the subjects with complete and accurate information as known before the trial begins, which is the prerequisite for subjects to make rational decisions on whether to participate in the research. With respect to the abstract review standards, whether the information conveyed by the researchers is "full" can be judged according to three criteria: (1) researchers determine the scope of information required on the basis of the best interests of the subjects; (2) researchers inform subjects of the risks, particularly those that are sufficient to make a reasonable person pause to consider whether to participate in the research; (3) the researchers inform the subjects of all available information related to the experiments.⁵

China has enumerated the elements necessary for informed consent. Article 14 of the "Good Clinical Practice" stipulates that, "The researchers or their designated representatives must describe the following specific circumstances of the medical trials to the subjects in detail: (1) the subjects participate in the trials voluntarily and have the right to withdraw at any stage of the trial without discrimination or retaliation and without affecting their medical treatment, rights, and interests; (2) the subjects must receive the commitment that their participation in the trial and their

personal data obtained during the trial are kept confidential...[w]hen necessary, the data of the subjects can be viewed by the drug supervision and administration departments, the ethics committee, or the sponsor according to the provisions; (3) [subjects shall be informed of] trial purpose, process and duration, operation and the expected benefits and risks of the subjects and that the subjects shall be informed of the possibility to be assigned to different groups of the trial; (4) the subjects shall be provided with sufficient time to consider whether to participate in the trials voluntarily and [researchers] shall describe and explain the above situation to the[] [subject's] legal representatives if [the subjects] hav[e] no ability to express the[ir] consent...the informed consent process shall adopt the language and text that can be understood by the subjects or their legal representatives, so that the subjects can understand the related information during the trial; (5) the subjects can get treatment and appropriate compensation in case of test damage."

The above requirements are still a bit weak; for example, they lack the obligation to disclose the "research funding source," a provision included in the "Declaration of Helsinki." If there is no opportunity to learn about the research's funding sources—and all the power and money entanglements behind the research institutions—subjects can neither understand who truly gains by the human experimentation nor fully evaluate any conflicts with their own interests.

In practical operation, the informed consent form shall be exhaustive and clearly inform subjects that the trial is clinical research conducted according to design procedures rather than a purely therapeutic measure; that subjects are likely to be assigned to the experimental group or control group randomly; that whether the experimental drug is superior to existing drugs is currently unknown; and that the subjects are likely to encounter unexpected risks. (After all, any kind of drug therapy is likely to produce adverse reactions, and participation in clinical research cannot rule out adverse reactions or other adverse events.) Subjects must make the decision to participate or not participate autonomously after careful consideration of the risks and potential benefits and must have the right to withdraw freely at any time without suffering discrimination or retaliation and without compromising their medical interests or personal information.⁶

⁴Y.F. Chen, R.Z. Qiu, *BIOMEDICAL RESEARCH ETHICS* (Beijing: China Union Medical University Press, 2003, at 111–116).

⁵R.Z. Qiu: *BIOETHICS* (Beijing: Renmin University Press, 2009, at 235–237).

⁶Y.P. Du, et al., *On the Interpretation of Drug Clinical Trials Informed Consent*, *JOURNAL OF TRADITIONAL CHINESE MEDICINE*, June 1, 2011, at 623–624.

B. Proper Understanding

Effective informed consent requires researchers to ensure that subjects have a proper understanding of the relevant information. By signing the informed consent form, the subjects indicate that they understand the medical interventions undertaken for them, or the clinical trial process they participate in, and all the circumstances related hereto. Informed consent, however, is not merely an end goal; rather, it is an educational process that occurs between researchers and possible subjects. Informed consent starts from the initial contact with a possible subject and continues throughout the whole process of the research. By providing possible subjects with all relevant information (including repeating and explaining it as necessary), answering their questions, ensuring each subject understands each procedure, and providing each subject with sufficient time to consider and make decisions (including time for discussion with their families or others), researchers obtain true informed consent and show respect for subjects' dignity and autonomy.

This process necessarily requires that the language and text of the informed consent form be the subjects' mother tongue and written in a way that is easy for laypersons to understand. Researchers shall inform subjects of the informed consent's content in detail, by means (whether oral or written) that can be readily understood by the subjects. The research team must ensure that subjects fully understand the potential risks and side effects; avoid ambiguous content and fuzzy speech; avoid inducement or coercion; and obtain the autonomous consent of the subjects. Researchers must also evaluate whether the information has been fully understood by the subjects, perhaps by administering oral or written tests. The informed consent dialogue or process must constitute "substantive communication between researchers and subjects," and its ethical or legal consequences are as follows: researchers must provide individualized, comprehensible, useful, and appropriate instructions according to the various subjects' specific circumstances, rather than simply seeking to prove that they have fulfilled their obligations in a *pro forma* way through obtaining a signed informed consent form.⁷

C. Voluntary Consent

Subjects make the decision to participate in, not to participate in, or withdraw from research voluntarily on the basis of a full understanding of the research's nature, purpose, procedures, benefits, and risks. The premise of voluntary consent is that subjects must have the capacity to give informed consent. In this regard, it is important to bear in mind that Chinese law does not prohibit minors from participating in human trials; whether to participate in human trials is decided by the minors and their guardians. Paragraph 3 of Article

15 in "Good Clinical Practice" stipulates that for children to be subjects, researchers must obtain the informed consent of the child's legal guardians or parents, who must sign the informed consent form on behalf of their children. Furthermore, the consent of the children themselves will be required if they can meaningfully make the decision as to whether to participate in the research. Whether a child's personal consent is required must be determined on a case-by-case basis.⁸

If physicians conduct experimental clinical trials on the patients without the consent of the patients or their family members, the health administrative departments shall do one or more of the following: give the physicians official warnings; suspend the physicians from medical practice for more than 6 months and less than 1 year; in cases of gross violations, revoke the physicians' practicing certificates (licenses); or affix criminal responsibility if the case is serious enough to constitute a crime. In the case of procedures resulting in damage or injury to the subjects, the implementers shall provide the subjects with appropriate compensation. The clinical trial contracts should specify compensation-related matters.

The informed consent documentation provided to subjects should include materials with all necessary information, including any/all materials that have been or would have been viewed by subjects (*e.g.*, recruitment advertisements, a "research profile," any useful or relevant audiovisual, electronic, or digital materials, etc.), as well as the informed consent form itself. In addition, if the clinical trial involves the use of subjects' biological specimens, the informed consent form shall also include a separate chapter or section concerning the collection and use of same. As a rule, recruitment advertisements shall neither mention the government supervision and management departments, nor promise any reward(s) for participation. Furthermore, screening inspection and biological specimen collection required before the clinical trials begin require two kinds of informed consent: one for collection and analysis of the biological specimens; and the other for participation in the test after meeting the inclusion standards. If the screening reveals any medical conditions, subjects should be informed as to such findings and advised to seek treatment as appropriate.

The following example concerns the aforementioned "Golden Rice event."⁹ The research group in

⁷H.S. Zhang, *et al.*, *Study on the Informed Consent of Human Medical Trials*, *ORIENTAL LAW*, April 1, 2013, at 126–134.

⁸X. He, *Extraction Perfect Legislation of Human Trials of Informed Consent in China*, *JOURNAL OF NANJING UNIVERSITY OF TRADITIONAL CHINESE MEDICINE* (social science edition), Nov. 1, 2010, at 158–162.

⁹X.M. Zhu, "Golden Rice Event" Is Entirely Cleared; The Concerned Person[s] Should Be Claimed Responsibility; available at <http://finance.qq.com/a/20121211/004955.htm> (last visited Oct. 12, 2013.)

charge of this project organized briefings of the students' parents and guardians before the test but did not explain that the test would use the genetically modified Golden Rice. Only the last page of the informed consent form, on which neither Golden Rice nor genetically modified rice was mentioned, was issued to be signed by the parents and guardians on site. The project leader deliberately used the expression "rice rich in carotenoid" and avoided use of the term Golden Rice when seeking signatures on the informed consent form. It is thus clear that the research group violated informed consent principles under Chinese law, and the consent obtained was illegal and invalid because it was based on inadequate experimental information, and subjects' parents/guardians could not understand the experiment.

II. ETHICAL REVIEW OF INFORMED CONSENT TO HUMAN EXPERIMENTATION

Informed consent and ethical review protect the interests of human trial subjects. As the external expression of respect for the subject's rights, the requirement for informed consent embodies the value placed on human beings, reflects a consciousness of human rights, and guarantees potential subjects the power to choose meaningfully whether to participate in research. Such a guarantee protects **all** parties—subjects and researchers alike, inasmuch as without proper (and documented) informed consent, researchers could face legal liability.

As an additional protection, informed consent materials must be reviewed by the ethics committee. Chinese medical review bodies are established inside research institutions. Article 6 of "Ethical Review Methods for Biomedical Research Involving Human[s]" stipulates that institutions carrying out biomedical research involving humans (including medical and health organizations, scientific research institutions, disease prevention and control centers, as well as maternity and child care institutions) set up institutional ethics committees responsible for ethical review and supervision of biomedical research and related technical application projects. Article 9 of "Good Clinical Practice" stipulates that an ethics committee shall consist of at least five persons of both sexes, including pharmaceutical professionals, non-pharmaceutical professionals, legal experts, and persons from other units. The composition and work of the ethics committee shall not be affected by those participating in the trials. The structure of Chinese medical review bodies is characterized by convenience and low cost, but such a review mechanism may fail because of the economic and academic temptations posed by human experimentation, which can affect the decision-making of ethical review committee members.¹⁰

The main elements of ethical review include: (1) whether the qualifications and experience of the researchers meet the experiment's requirements; (2) whether the research program meets ethical principles and scientific requirements; (3) whether the expected benefits of the research are weighed against the possible risks encountered by the subjects; (4) whether the subjects (or their families, guardians, and legal representatives) are provided with complete and understandable information in the process of informed consent and whether the methods used to obtain informed consent are appropriate; (5) whether confidentiality measures are taken to protect the personal and medical information of subjects; (6) whether the inclusion and exclusion criteria for the subjects are appropriate and fair; (7) whether subjects are clearly informed of their rights, including the right to withdraw from the research at any time without penalty; (8) whether subjects receive reasonable compensation for participation in the research, and whether they will be provided with appropriate treatment and compensation measures if they are injured (or even die) as a result of their participation in the research; (9) whether there are specified researchers with designated responsibility for informed consent and security issues; (10) whether the subjects are provided with protective measures against the trial's risks; and (11) whether there are conflicts of interest between the subjects and the researchers.¹¹

Researchers must be approved or licensed before the start of medical experiments. Any modifications to the test programs during the test must be approved by the ethics committee. Serious adverse events occurring during the test must be reported to the ethics committee in a timely manner. Researchers and sponsors must make certain that sufficient relevant scientific literature has been provided as the basis for research involving human subjects and must be certain the research design conforms to generally accepted scientific principles.¹²

In the Golden Rice event, the single trial item was subject to ethics review once a year, and the changes in the item content were subject to re-examination according to the provisions of Tufts University. There were significant informed consent problems with the event. On June 2, 2008, the Tufts University Ethics Committee approved the Chinese version of the NIH project informed consent, but the project leader sought informed consent from the subjects in advance, on

¹⁰H.J. Shen, *Legal Regulation of Juvenile Human Trials from "Golden Rice" Event*, JOURNAL OF LAW SCIENCE, Nov. 1, 2012, at 54–64.

¹¹See Article 20, "Ethics Review Rule of Biomedical Research Relates to the People," published by China Ministry of Health.

¹²P.P. Dong, et al., *Research on the Establishment of Medical Ethics Review of the Regulatory System*, MEDICINE AND PHILOSOPHY, Apr. 1, 2013, at 28–29.

May 22, 2008, in violation of the provisions. The project also passed review in the Ethics Committee of Zhejiang Academy of Medical Sciences at the end of 2003, but the trial was not conducted within the allowed time limit.¹³

The ethics committee should review the subjects' informed consent from the following perspectives: (1) protecting the rights and interests of the subjects while ensuring that the written informed consent form meets the requirements of "Good Clinical Practice" and guaranteeing the confidentiality of subjects' information and protection of their privacy; (2) ensuring that subjects clearly understand the trial purpose and methods, and also ensuring that there are emergency preparedness measures in place for potential problems; (3) allowing subjects to withdraw from the study at any time without prejudice; (4) making sure that the trial design protects subjects from damage as much as possible (or at least minimizes damage), and that the trials will be immediately terminated if it causes serious injury to the subjects; (5) requiring subjects who can understand the trial (and their risks) but who cannot sign their names (*e.g.*, illiterate subjects or subjects with certain disabilities) to signal consent by some other mechanism, such as thumbprints (or alternately, requiring appropriate family members to signal consent for the subjects); (6) respecting the subjects' opinions if they do not agree to participate in the trials, even if their family members agree to allow the subjects to participate.¹⁴

The Golden Rice experiment site is in Hunan, China, and the Ethics Committee of Tufts University and Zhejiang Medical Ethics Committee arguably did not properly consider the benefits to this distant Chinese trial location in their review. Article 6.2.6 of WHO's "Guidelines of Ethics Committee on Biomedical Review" stipulates that community factors shall be considered in ethical review, including "research impact and relevance caused by extraction of subjects from local communities or relevant communities"; "steps of relevant community counseling in the trial design phase"; "impact of community on personal consent"; "community counseling proposed in the research process"; "contributions of research to enhancing local capacity, such as enhancing local medical care, and the coping capacity of the research with the public demand"; and other like aspects. After the trial, matters of concern include "accessibility and affordability of successful research projects in relevant communities" and "methods for the subjects and relevant communities to obtain the trial research results." In the ethics review of the Golden Rice trial, whether the trial can meet the special health needs in the trial location, whether the trial can bring benefits to the subject students (and also to subject schools, as well as to other children similar to the experimental subjects), and whether the experimentalists have conducted full consultation with the schools and local communities will all affect the effectiveness. Therefore, it is necessary to strengthen the supervision of

the ethics committee(s) over ongoing trials in China, and also to stipulate that the ethics committee shall investigate at the trial site, including observing the trial process, having direct contact with the subjects, and fully understanding the informed consent process so as to confirm its legitimacy and validity.¹⁵

The ethics committee should also focus on the safety of the trial; the reasonableness of the research design and statistical methods; the possibility of obtaining reliable conclusions with the fewest subjects; whether the expected benefits exceed the predictable risks to and inconvenience of the subjects; the procedures for subjects to withdraw from the trial; the basis for the application of control groups in the trial; standards to suspend or terminate the entire research project if necessary; provisions for monitoring and reviewing the research implementation process; appropriate research venues and staff (including auxiliary personnel, trial facilities, and emergency measures); research reports and publication.

The Golden Rice trial involved the safety of genetically modified food. The international environmental organization Greenpeace, which opposes genetically modified agricultural products, stated, in its report on uncovering the secrets behind Golden Rice, that in its opinion, children are not appropriate experimental subjects for "transgenesis" (consumption of modified foods); that "genetically modified food" poses potential risks to human health; and that it was "inconceivable" that a U.S. agency tested genetically modified rice with (or on) Chinese children."¹⁶

Despite the concerns of Greenpeace and others, some experts believe that the chemical composition of the Golden Rice is basically the same as that of ordinary rice, only with the β -carotene content slightly higher, which will not cause harm to the subjects, and that the rice used in the trial has been proved safe by a large number of preclinical trials (including experimental toxicology research) and multiphase clinical trials (human safety research).¹⁷ No harm was seen to the children in the trial. This paper does not take a position on the safety of Golden Rice as such, but notes that it is necessary that researchers and sponsors make complete

¹³Y.H. Huang, "Matters Behind the Golden Rice Event Ethical Review," *New Peking Newspaper*, Sept. 7, 2012.

¹⁴X.D. Zheng, *et al.*, *On the Ethical Review of Medical Research Affairs*, *JOURNAL OF SECOND MILITARY MEDICAL UNIVERSITY*, Dec. 1, 2007, at 20–23.

¹⁵X.C. Chen, *The Ethics Review Committee Supervision System*, *JOURNAL OF NANJING MEDICAL UNIVERSITY (Social Science Edition)*, June 1, 2011, at 21–25.

¹⁶Greenpeace. *Opened the "Golden Rice" Secret—Children Should Not Be Transgenic Experiment Object[s]*; available at www.greenpeace.org/china/zh/news/stories/food-agriculture/2012/08/golden-rice/ (last visited Oct. 1, 2013).

¹⁷L.D. Li, Y.K. Li, "'Golden Rice' Should Not Be Spurn[ed]," *Chinese Science News*, Sept. 19, 2009.

and truthful statements to the ethics committee when conducting ethics review, so that the committee can make reasonable decisions. However, the informed consent form approved by Tufts University in 2008 did not mention that the test material was the “genetically modified rice” and just called it “Golden Rice.” (The informed consent form for the research previously approved by this university’s ethics committee from 2003 to 2006 had described the Golden Rice as “genetically modified rice.”) Approval of the 2008 form by the Tufts University ethics committee was adverse to Chinese subjects’ ability to fully understand the experiment because it did not provide complete information—*i.e.*, that the Golden Rice was genetically modified rice. Moreover, the Golden Rice used in the project had not been declared and approved when brought to China from abroad, violating the provisions of Article 31 in China’s “Regulation on the Safety Administration of Genetically Modified Organism[s] in Agriculture.”¹⁸ The project also concealed from the Chinese ethics committee and the informed consent process the fact that genetically modified rice was to be used in the trial, which violated the ethical review requirements.

III. CONCLUSION

With the rapid development of Chinese biomedicine in recent years, the amount of human ex-

perimentation is increasing. In addition, foreign pharmaceutical companies and research institutions have carried out transnational human trials in China, leading to many “hot” social events, such as the AIDS vaccine test¹⁹ and the Berlin heart test.²⁰ With “hot button” issues such as “transgenosis,” “American universities,” and “Chinese children” (among others), the Golden Rice test aroused unprecedented social concern.

Human trials of genetically modified food, no matter when they are conducted, should be applied for in strict accordance with the relevant management procedures and should be conducted only after the deliberation, evaluation, and approval of the special ethics committee. Throughout any such experiment, the researchers and sponsors must earnestly safeguard the human rights of the subjects, in strict accordance with all relevant legal provisions on informed consent and ethical review. However, besides pointing out improprieties on the part of researchers or sponsors, the Golden Rice event also exposes deficiencies in China’s human experimentation legislation and practice. China must speed up revising and improving its human experimentation legislation, as well as improving its rules on informed consent, the structure of the ethics committees, and how ethics committees supervise human experimentation.

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¹⁸See Article 31 of “Regulations on Safety Management of Agricultural Genetically Modified Organisms.” In order to introduce agricultural genetically modified organisms from outside the People’s Republic of China for research or testing, the importer must submit an application to the Agricultural Administrative Department of China.

¹⁹2005-6-9 Z. Shun *et al.*, “The AIDS reagent mystery,” *China News Weekly*, July 9, 2005.

²⁰2007-7-25 C. Yu, “Shanghai East Hospital Artificial Heart Operation and Foreign Institutions Medical Body Test in China,” *Southern Metropolis Daily*, June 25, 2007.