Ethical Issues concerning the Protection of Children in Biomedical Research in Japan

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Current Japanese Situation regarding Biomedical Research in which Children will participate as Human Subjects

Recently, research on the problems of childhood mental developmental disorders such as ADHD (attention deficit/hyperactivity disorder) from a medical and neuroscientific perspective has been pursued in Japan. Accordingly, opportunities for children to participate in clinical research as human subjects are rapidly increasing.

And, as such, the problems of protecting children involved as human subjects in clinical research are becoming considerably important. The reasons stem from the fact that children, because of their age, have reduced capacity to comprehend, and lack the legal capacity to consent to enrollment in research as human subjects. Therefore "the protection of children as human subjects" becomes more important than the protection of adults in Japan.

Backwardness in Embracing the Protection of Children Involved as Human Subjects in Japan

Nevertheless, Japan has fallen far behind the US and Europe in implementing the protection of human subjects' rights. As a matter of fact, Japan handles many problems concerning the protection of children as human subjects with only the following two guidelines.

(1) "Guidance on Clinical Investigation of Medical Products in the Pediatric Population" based on the agreement at the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) [1]

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1 "Guidance on Clinical Investigation of Medical Products in the Pediatric Population" deals with "Ethical Issues in Pediatric Studies" thematically. This guidance clearly specifies that "the pediatric population represents a vulnerable subgroup. Therefore, special measures are needed to protect the rights of pediatric study participants and to shield them from undue risk."

(2) "Ethical Guidelines for Clinical Studies" announced by the Ministry of Health, Labor and Welfare in July 2003 (amended December 28, 2004)

Unfortunately, there are no ethical guidelines that take into account children as human subjects thematically.

In addition, the "Ethical Guidelines for Clinical Studies" have not been decided through analyzing historical events and national debate. And there are no punishments in place if a researcher violates those guidelines. There is little description of the protection of children in biomedical research. Therefore, there is a pressing need to prepare ethical regulations concerning the protection of children involved as subjects in research in Japan.

Development of Legal Frameworks for Children as Human Subjects in Biomedical Research Delayed in Japan

Until now, Japan has lacked the viewpoint of developing protection regulation for children as human subjects. Why has the implementation of protection regulation for children as human subjects been delayed in Japan so far?

The main reason is the ambiguity of the legal position of "children" in medical practice. For example, in the first place, "consent" in medical practice is not a juristic act but a factual act. And a medical contract between the physician and patient is a quasi-mandated contract. Therefore, it is natural that the legal position of consent to participate in biomedical research is unclear in Japan.

Such situations are remarkably manifest even in research in which children participate in as human subjects. In Japan, it is a basic stance that a minor who lacks the legal capacity to consent to enrollment in research as a human subject must obtain the consent of his/her statutory agent to perform any juristic act. So in Japan, the legal position of a child's consent (assent) to participate in biomedical research is very ambiguous. [1]

Then, how should Japan establish concrete ethics regulations concerning the protection of children involved as human subjects in clinical research?

Until now, the U.S. and Europe have considered improving the legislation vouching for the validity of biomedical research from various viewpoints circumstantially; furthermore, the U.S. has dealt with research in which children as "disadvantaged members of society (socially vulnerable subjects)" participate as human subjects by establishing additional protection regulations for children involved as human subjects in research. Japan should also consider

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1 The Civil Code specifies that the "age of majority is reached when a person has reached the age of 20 (Article 4. Age of Majority)" and a "minor must obtain the consent of his/her statutory agent to perform any juristic act; provided, however, that, this shall not apply to an act merely intended to acquire a right or to be relieved of a duty" (Article 5, Juristic Act of Minors).

protection regulation for children as human subjects by examining efforts to protect children as human subjects in various foreign countries, especially in the U.S.

International Movements concerning the Protection of Children Involved as Human Subjects in Clinical Research

In Japan, the "Declaration of Helsinki" is required to be followed by ministerial ordinance on the "Guideline for Good Clinical Practice (1998)".

Article 24 of this declaration states that "for a research subject who is legally incompetent, physically or mentally incapable of giving consent, or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law." These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.[1]

Similarly, the "International Ethical Guidelines for Biomedical Research Involving Human Subjects" prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) also clearly specify that "before undertaking research involving children, the investigator must ensure that: (1) the research might not equally well be carried out with adults; (2) the purpose of the research is to obtain knowledge relevant to the health needs of children; (3) a parent or legal representative of each child has given permission; (4) the agreement (assent) of each child has been obtained to the extent of the child's capabilities; and (5) a child's refusal to participate or continue in the research will be respected."

In addition, these ethical guidelines provided the new perspective of "deliberate objection by a child" regarding the protection of children in research.[2]

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1 In addition, this declaration refers particularly to the "child's assent" and "research on individuals from whom it is not possible to obtain consent." "When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative" (Article 25). "Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population" (Article 26).

2 In the "Commentary on Guideline 14," this guidelines point out specifically that a "deliberate objection by a child to taking part in research should always be respected even if the parents have given permission, unless the child needs treatment that is not available outside the context of research, the investigational intervention shows promise of therapeutic benefit, and there is no acceptable alternative therapy."

Protection Regulation for Children as Human Subjects in the U.S.

And now, it is a well-known fact that the U.S. has not yet ratified the "Convention on the Rights of the Child (1989)." However, the U.S. has uniquely examined the protection regulation for children as research participants in detail from a variety of different angles. As for the institutional design of biomedical research, Europe has been significantly influenced by the U.S.

A. "Research involving children: Report and recommendation (1977)"

This report was proposed by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1977.

This report discusses biomedical research with no prospect of direct medical benefits to the child from the standpoint of "risk-benefit-balance analysis" in detail for the first time.

B. "The Belmont Report: Ethical principle and guidelines for the protection of human subjects of biomedical and behavioral research (1979)"

"The Belmont Report: Ethical principle and guidelines for the protection of human subjects of biomedical and behavioral research" is a very important report in considering the protection of children in biomedical research in the U.S.

This report considered (a) the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects, (b) the boundaries between biomedical and behavioral research and accepted and routine practice of medicine, (c) the role of assessment of risk-benefit criteria in determining the appropriateness of research involving human subjects, (d) appropriate guidelines for the selection of human subjects for participation in such research, and (e) the nature and definition of informed consent in various research settings.

C. "Code of Federal Regulations, Title 45 Public Welfare, Part 46 Protection of Human Subjects: 45CFR46, Subpart D Additional Protection for Children Involved as Subjects in Research (1983)."

The Department of Health and Human Services (DHHS) has dealt with research in which children as "disadvantaged members of society (socially vulnerable subjects)" participate as human subjects by establishing this additional protection regulation for children involved as human subjects in research.

A central feature of Subpart D is the classification of research activities based on an analysis of probable risks, possible benefits, and associated discomfort. Specifically, in Subpart D, research activities are classified into the following four categories.

(1) Research not involving greater than minimal risk

This category is defined as "the probability and magnitude of harm or discomfort anticipated in the proposed research is not greater, in and of itself, than ordinarily encountered in daily life or during the performance of routine physical or psychological examinations and tests (45 CFR 46, Section 102 (i))."[1]

(2) Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects

On this occasion, the IRB must determine (a) whether such risk is justified by the anticipated benefit to the subject, (b) whether the risk/benefit relationship to the subject is as favorable as for alternative approaches, and (c) the assent of the subject.

(3) Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about a subject's disorder or condition

This is an approvable category if (a) the risk is a minor increment over minimal risk, (b) the inherent research protocol is within the medical and other procedures that the subject may experience, (c) the procedure produces generalizable knowledge, and (d) the assent of the child is secured.

(4) Research not otherwise approvable that presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

This is an unapprovable category of research with children. However, under certain circumstances and after referral to the DHHS, the secretary may approve the protocol if the research outcome would help to understand and contribute to the general welfare of children.

D. American Academy of Pediatrics "Informed Consent, Parental Permission, and Assent in Pediatric Practice (1995)"

In this statement, the AAP provides an updated analysis of (a) the concept of informed consent, (b) the ethics of informed consent and the concept of the right to refuse treatment (dissent), (c) the concept of "proxy consent," (d) the concept of parental permission and child assent ("assent" has no legal basis)[2]; and (e) informed consent of adolescents ("legal

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1 This definition of minimal risk is the same for all human subjects, whether children or adults. The National Commission has mentioned examples of minimal-risk research protocols for children, such as surveys, noninvasive physiological monitoring, routine immunization, and obtaining blood and urine samples. This category, if it meets all other conditions, can be approved by the IRB.

2 "Assent" should include at least the following elements: (1) helping the patient achieve a developmentally appropriate awareness of the nature of his or her condition; (2) telling the

emancipation," "emancipated minor"[1]).

E. "NIH (National Institutes of Health) Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects (1998)"

This document sets forth guidelines on the justifications for exclusion of children from research. For example, it is expected that children will be included in all research involving human subjects unless one or more of the following exclusionary circumstances can be fully justified: (a) the research topic to be studied is irrelevant to children; and (b) insufficient data are available in adults to judge the potential risk in children.

Five Points of View to Consider in Regulations for Protecting Children as Human Subjects in Japan

So, for the reasons stated above, five points of view that Japan should pay attention to in considering regulations for protecting children as human subjects become clear. [2]

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patient what he or she can expect with tests and treatment(s); (3) making a clinical assessment of the patient's understanding of the situation and the factors influencing how he or she is responding (including whether there is inappropriate pressure to accept testing or therapy); and (4) soliciting an expression of the patient's willingness to accept the proposed care. Regarding this final point, we note that no one should solicit a patient's views without intending to weigh them seriously. In situations in which the patient will have to receive medical care despite his or her objection, the patient should be told that fact and should not be deceived.

1 Definitions of "emancipated minor" include: (1) one who is self-supporting and/or not living at home; (2) married; (3) pregnant or a parent; (4) in the military; or (5) declared to be emancipated by a court. Second, many states give decision-making authority (without the need for parental involvement) to some minors who are otherwise unemancipated but who have decision-making capacity ("mature minors") or who are seeking treatment for certain medical conditions, such as sexually transmitted diseases, pregnancy, and drug or alcohol abuse. The situations in which minors are deemed to be totally or partially emancipated are defined by statute and case law and may vary from state to state. Legal emancipation recognizes a special status (e.g., independent living) or serious public and/or individual health problems that might not otherwise receive appropriate attention (e.g., sexually transmitted disease).

2 Cf. Chieko Kurihara, "Ethics in research involving children: introduction Historical review over ethical dilemma and regulatory development in the world ", in : Rinshou Hyoka (Clinical Evaluation),Vol.34(1),2007,p.103-22. (in Japanese)

(1) Children's rights and the ethical dilemma of involving them in clinical research

(2) Key concepts such as "assent," "parent's rights permission," " proxy consent," and "emancipated minor"

(3) Cases where the parent's consent/permission may be waived

(4) Risk-benefit analysis and conditions where research involving children could be authorized

(5) Necessity for a third-party institution that evaluates fairness in research[1]

Movement for Legislation for the Protection of Human Research Participants in Japan

There are some new pushes in Japan to consider legislation for the protection of children as human subjects based on the recent international movements of legislation for the protection of human research participants.

A. Ministry of Health, Labor and Welfare Panel on Clinical Trials (2005)[2]

Various petitions calling for legislation for the protection of human subjects in research were submitted to this panel and examined as the subject of future investigation.

B. Cabinet Office, Government of Japan "Council for Science and Technology Policy"[3]

Furthermore, at this council, the goal of raising "Ethical Guidelines for Clinical Studies (2003)" to the same level as ICH-GCP invested with legal binding power was indicated clearly.

C. Japan Science and Technology Agency, Center for Research and Development Strategy "Strategic Recommendations concerning Clinical Research: with the aim of radical reform of our domestic system of clinical research"[4]

This report gives the highest priority to basic legislation on clinical research.

At any rate, why is legislation for the protection of children as human subjects required in Japan? I believe there are three main reasons:

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1 In Japan, there is no research review board to serve as a public body that is independent of research institutions.

2 Cf. http://www.mhlw.go.jp/shingi/2005/05/dl/s0526-2e.pdf (in Japanese)

3 Cf. http://www8.cao.go.jp/cstp/siryo/haihu62/siryo1-2.pdf (in Japanese)

4 Cf. http://crds.jst.go.jp/output/pdf/06sp08.pdf (in Japanese)

(1) Absence of effective enforcement of the law that prohibits research using a human subject without "his/her consent."

(2) Except for regulations for clinical trials, there are no comprehensive regulations with binding force that protect human subjects in research, either. Administrative guidelines without disciplinary regulations concerning misconduct of researchers cannot ensure the protection of human subjects.

(3) In Japan, there are no autonomous organizations inside the professional group (Japan Medical Association) that examine and impose disciplinary action. The JMA is a professional profit organization based on voluntary admission. Therefore, not all physicians are members of the JMA. In other words, its cohesion as an organization of the medical profession in Japan is very fragile.

Conclusion: Importance of the Institutionalization of Research Ethics Education

As mentioned above, in Japan, a comprehensive management system that protects human subjects including children in research should be promoted by establishing a research participants' protection law.

However, by only establishing disciplinary regulations concerning misconduct of researchers, assurance of fairness in biomedical research cannot be expected in Japan.

In addition, Japan has to constantly promote the institutionalization of research ethics education to embody the establishment of a human subjects' protection system in the future. In fact, NIH added a new point of view on research ethics education to embrace the protection of human research participants in 2000.1 The guideline states that the NIH will require education on the protection of human research participants for all investigators submitting NIH applications for grants or proposals for contracts or receiving new or non-competing awards for research involving human subjects. There is no doubt that Japan has to acquire this standpoint on research ethics education as rapidly as possible.

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1 Cf. http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html