Compensation and Insurance for Participants/Subjects Harmed in Clinical Research Studies: Process of the inheritance of Good Clinical Practice (GCP) in Japan and its present status*1

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Introduction

The following sentence was added to paragraph 14 of the Declaration of Helsinki (DoH) of the World Medical Association (WMA) when it was revised in the General Assembly held in Seoul in 2008: "The protocol should include … provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study."[1] Provisions guaranteeing (assuring) free treatment and compensation for loss to participants (subjects) who suffer injury (harm) as a result of participation as a volunteer in clinical research (hereinafter "treatment and indemnity provisions") is at the core of the protection of subjects, because it is only when free treatment and indemnity are implemented in tangible form when something has gone wrong that the protection of subjects is brought to conclusion.

This paper gives an overview of Japan's initiatives to address this issue over the past dozen years or so. It shows that the present situation in Japan is still only halfway to the ideal and that improvements need to be made immediately. I am fully aware that it is difficult to produce a uniform conclusion, since the necessity and degree of compensation is closely related to the economic condition, medical system, and social security system of each country. However, I wish to make the point that the DoH's indemnity clause needs to be reinforced in the future, if thought is to be given to the thorough protection and defense of subjects.

Table 1 provides a list of conclusions. Japan's regulatory authorities have established standards that differentiate participants (subjects) in clinical research into subjects covered by the Pharmaceutical Affairs Act and subjects not covered by that act. The former standards are called Good Clinical Practice (GCP) and the later standards are called Ethical Guidelines on Clinical Research. As is clear when comparing the middle and right-hand columns of the table, the later regulations are too weak and do not provide sufficient subject protection. I urge relevant parties to reflect seriously on this.

Origin of and Changes in Japanese GCP

From the end of World War II in August 1945 until the GCP for Trials on Drugs (Notification) issued in 1990 by the Director of the Pharmaceutical Affairs Bureau of the Ministry of Health and Welfare took effect, a number of cases of adverse drug reaction-induced suffering that shocked the public were brought into the courts

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Table 1 Status of compensation in Japan in clinical research subject to ICH-GCP

	GCP ministerial ordinance		Ethical guidelines on clinical research
Subject to	Clinical studies (trials) covered by the Pharmaceutical Affairs Act		Other clinical studies
Subjects	Healthy individuals	Patients	Healthy individuals/patients
Compensation	Yes	Yes	Provision exists, but "without compensation" accepted
Content/degree	Similar to the occupational accident relief system (grade 1 to grade 14)	Similar to the adverse drug reaction relief system (excludes grades 8 and below from the occupational accident system and anticancer drugs)	Actual condition is chaotic
Backed up by insurance	Yes	Yes	Insufficient/undeveloped
Type of insurance	Treatment only	Treatment only	
	Combined with product liability insurance, etc.	Combined with product liability insurance, etc.	

Table 2 Changes in the Pharmaceutical Affairs Act in Japan, etc.

1960:	(New) Pharmaceutical Affairs Act enacted
1961:	Universal health insurance coverage launched
1964:	World Medical Association (WMA) Declaration of Helsinki (DoH) adopted
1971:	Drug efficacy reevaluation system introduced; sale of Dihydro SM and Compound SM suspended
1975:	Revisions to WMA DoH adopted in Tokyo
1977:	Judge Kabe of the Tokyo District Court issued a settlement proposal in the SMON case.
1979:	Major revision of the Pharmaceutical Affairs Act; Adverse Drug Reaction Sufferings Relief Fund Law enacted
1989:	Good Clinical Practice (GCP) for Trials on Drugs (Notification) issued by the Director of Pharmaceutical Affairs Bureau, Ministry of Health and Welfare of Japan
1990:	Manual of GCP for Trials on Drugs published

(**Table 2**). These included: thalidomide; streptomycin (SM) hearing loss and shock death; SMON (subacute myelo-optic neuropathy) caused by chinoform (clioquinol); quadriceps and other muscle contracture resulting from intramuscular injection of chloramphenicol, etc., in infants; and chloroquine retinopathy. In these cases, the trials between the patients/plaintiff's groups seeking early relief from harm and the defendant pharmaceutical companies/national government, which denied a causal association, were dragged out remarkably, becoming a cause of public anxiety. The courts repeatedly pointed out the negligence of the pharmaceutical affairs administration in their rulings and in the trail process (e.g. the Kabe Recommendations in the SMON case), making modernization of the drug development process an urgent issue.

As a result, the Pharmaceutical Affairs Act legislated in 1960 was drastically revised in 1979, creating the adverse drug reaction relief system. Nearly 10 years later, the Pharmaceutical Affairs Act was revised again following the International Conference on Harmonization of

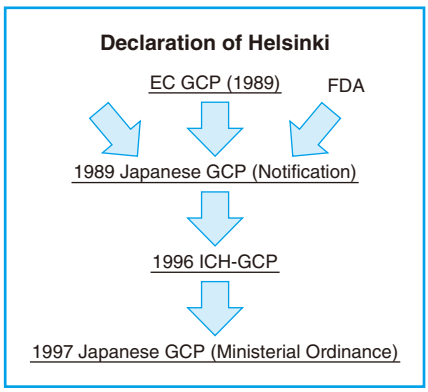

Fig. 1 Origin of Japanese GCP

Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)-GCP Yokohama Accord, introducing a legal GCP system into Japan and finally catching up to the level of advanced Western nations. In 1961, universal health insurance coverage was launched, enabling the whole nation, rich and poor alike, to easily obtain the benefits of modern medicine and making Japan into one of the healthiest and longest lived countries in the world. On the flip side of this positive it can be said, from a retrospective point of view, that a negative appeared in the numerous cases of drug-induced suffering, resulting in part from the fact that insurance made a wide range of drugs available for use without financial burden on patients.

Origin of Japanese GCP

Although limited to clinical trials for the purpose of obtaining manufacturing approval for drugs (**"Chiken"** in Japanese), the GCP for Trials on Drugs of October 1989 was the first official standard in Japan related to the conduct of clinical trials. The word "GCP" and the name "Declaration of Helsinki" were introduced and publicized as a set at that time, and so these two terms were spread at a single swoop among physicians and researchers at university hospitals and national base hospitals concerned with drug development (**Fig. 1**).

The 1989 GCP (old GCP) was elevated to a legal system with substantially revised content at the time the Pharmaceutical Affairs Act was amended in 1997. Its name was changed then to the Ministerial Ordinance on GCP, which brings us up to the present. The old GCP was created based upon the 1989 European Community (EC)-GCP proposal, US Food and Drug Administration (FDA) regulations, and other references. The same as with informed consent, it is a concept that originated in Europe and the US and was absent in Japan. The 1997 Ministerial Ordinance on GCP incorporated the ICH-GCP (6), which was the outcome of the ICH agreed to by the European Union (EU), Japan, and the US in Yokohama in May 1996 (**Fig. 1**).

"Treatment and Compensation for Health Damage" Provision

At the time the GCP came into effect in 1989, the government already required study sponsors to assume no-fault liability and immediately provide reasonable and adequate compensation to subjects harmed as a result of study participation and to state such in the consent forms obtained from and information sheets given to subjects. It also requested study sponsors to take out compensation insurance for that purpose. It was not until much later that compensation insurance was launched, but clauses promising compensation were inserted into consent and information sheets from early on.

The following is the most commonly used provision for "treatment and compensation for health damage" used in consent and information sheets related to clinical trials:

"Please consult your primary doctor immediately if you develop symptoms during this trial that you did not have before. Appropriate treatment and appropriate measures shall be taken if you suffer an adverse effect or other health damage during or after participation in this trial. You may also receive compensation according to the type and degree of health damage.

However, please be aware that you may not receive compensation if it is found that you did not follow your primary doctor's instructions or that the health damage was due to your own carelessness."

Standards for Determining the Amount of Compensation

The above consent and information sheet states, "You may receive compensation according to

type and degree of health damage." At the time the old GCP was launched, an agreement was formed among the relevant parties to provide this compensation using the standards of the Industrial Accident Compensation Insurance Act as the standards for determining the amount of compensation for subjects of phase I clinical trials, and it was implemented as mentioned above.

By the way, Japan has developed a compensation system that covers a victim's loss to a certain limit in exchange for not requiring proof of negligence, with the aim of providing relief for the victim, apart from tort liability that questions negligence and provides indemnity for gross damages. Occupational accidents are one example, which have a compensation system based on the Industrial Accident Compensation Insurance Act. As a rule of thumb, this system determines the amount to be paid (compensation) by removing consolation money from the gross damages items, dividing the degree of harm (loss of a capacity to work = after effect) into 14 levels (grades), and taking the grade into consideration, with average wages as base. This is the model for many compensation systems (the Automobile Liability Security Act uses the above occupational accident compensation system in certification of after effects impediment).

Compensation provided under the industrial accident compensation system is commonly called the 70% payment; the amount is set at approximately 30% less than the full damages that would be paid if an action for damages were brought to the court. The distinctive feature is that, in lieu of full payment the subject (worker) will receive payment of compensation quickly, even if the employer was not negligent.

Since the accident-based method of determining the amount of compensation formed for healthy people could be used sufficiently in the cases of phase II and phase III trials, the author has insisted that it should be used and has obtained much agreement.[2,3] The problem is the amount of compensation for research that seeks a slight prolongation of life for the elderly and people in the end-of-life stage who have no possibility of being employed; I think that the amount of compensation should be determined in keeping with the actual condition, taken as an exceptional case.

Recently, however, while using the language of the "Treatment and Compensation for Health Damage" Provision in the text of consent and information sheets for phase II and phase III trials on patients, some pharmaceutical companies in Japan have created separate documents stating the company's thinking on compensation, starting a trend of substantially restricting the content of compensation, with other companies following suit. What these companies have brought in to restrict the content of compensation is the standard of compensation established for the adverse drug reaction relief system for marketed products. This standard **substantially curtails the compensation for injured parties with an after effects impediment grade of 7–8 or less in the industrial accident compensation system (traffic accident standard) and the compensation for injured parties in clinical trials on anticancer agents and biological products**. Guidelines issued by the Japan Pharmaceutical Industry Legal Affairs Association serve as the basis for the standard.[4]

At present, it is into anticancer agents and biological products that pharmaceutical companies are making huge investments in research. At any rate, I will point out here that it is wrong to bring the system of compensation for harm caused by adverse reactions to drugs sold on the market in large quantities into the compensation system for victims for the development of drugs (including anticancer agents and biological products).

The reasons this kind of unjust trend got started are the fact that some of the relevant parties have a complete lack of understanding about what constitutes "reasonable compensation" for research subjects, the fact that there are no legal provisions about the content and limits of compensation systems, even though they are being introduced, and the fact that the regulatory authorities, who have final responsibility in this problem, continue to remain mute with a wait-and-see attitude.

Present Status of Compensation Insurance

At present, pharmaceutical companies that conduct trials based on the Pharmaceutical Affairs Act invariably take out liability insurance covering compensation for loss up to the highest amounts of compensation provided by the

Table 3 Statements concerning compensation amount on the face and reverse of an insurance policy

Face

Amount payable: Bodily injury liability per person: 100 million yen; per accident: 300 million yen; during the insurance term: 300 million yen (3 million USD)*

Deductible: Per accident: 500,000 yen (5,000 USD)*

Notes: Clinical Trial Liability Insurance Rider

- Per accident, during insurance term: 300 million yen (coverage for bodily injury liability per accident, payment within the limit during the insurance term)
- Coverage limit per victim; as shown on "Reverse" (no exemption from responsibility)

Reverse

Coverage limit per subject

Degree of health damage: trial on healthy individuals

Payment limit (per subject)

- **Death: 30 million yen**
- **After effects impediment**

Grade 1: 90 million yen	Grade 6: 50 million yen	Grade 11: 15 million yen
Grade 2: 90 million yen	Grade 7: 40 million yen	Grade 12: 10 million yen
Grade 3: 70 million yen	Grade 8: 32 million yen	Grade 13: 7 million yen
Grade 4: 65 million yen	Grade 9: 25 million yen	Grade 14: 4 million yen
Grade 5: 55 million yen	Grade 10: 20 million yen	

- Lost work time compensation payment: 13,000 yen per subject per day for the period beginning on the fourth day of no wages due to lost work time.

*US dollar/JPY exchange rate: US$1≒100 yen.

occupational accident compensation system and the adverse drug reaction relief system, respectively. This is because they are required to submit the proposed subject consent and information sheet and the certificate of insurance coverage issued by an insurance company to the institutional review board.

There are three major types of insurance that pharmaceutical companies currently buy. The first is comprehensive liability insurance, which is bought by foreign pharmaceutical companies and some major Japanese pharmaceutical companies. This provides adequate coverage for clinical trials in addition to product liability for over-the-counter drugs and things such as insurance against fire at plants. The second type is healthy subject compensation insurance, which is insurance for clinical trials conducted on healthy people. It provides relief up to after effects impediment grade 14 in addition to death. Statements concerning compensation amounts on insurance policies are shown in **Table 3**.

In the case of the elderly and subjects who lack the ability to work because of a disability or other cause, the amount of compensation cannot be determined by focusing on the ability to work (or degree of loss thereof). Therefore, the time has come to think of a way to determine the amount of compensation in those kinds of situations. Some foreign pharmaceutical companies are grappling seriously with the issue of compensation in the case of clinical trials on anticancer agents in pursuit of slight prolongation of life and have released their results. One such example would be a paper written by Nabeoka Yuzo.[5]

However, it is incorrect to say that all work ability is lost because someone is a patient. While there are differences depending on the type of disease or injury, a person may not regain the same ability as a healthy person even if they get over the disease or injury, but it is not uncommon, for example, to regain no more than 50%–30%. If this kind of patient participates in a trial/study and unfortunately ends up with lost or reduced ability to work, it would be good to provide compensation at a rate, for instance, of 100% − 50 = 50% or 100% − 70 = 30%. This kind of calculation is routinely used in the practical business of trials when calculating the amount of compensation for damages caused by a medical error or

traffic accident. If this way of thinking were adopted, the single table used as the basis for compensation in occupational accidents would be enough plus the need to think separately about exceptional cases in which a patient has zero ability to work, as stated in the beginning.

However, as a third type, some pharmaceutical companies have introduced a compensation system for clinical trials on patients that uses the adverse drug reactions injured party compensation system. Insurance companies sell this type of insurance based on user requests. **Table 4** shows one example of this kind.

The expressions and amounts given here for death or impediment grade are exactly the same as the expressions and content of the adverse drug reactions injured party compensation system. Compared with the above healthy people, the amounts have been curtailed substantially, to 20 million yen versus 30 million yen in the case of death and 70 million yen versus 90 million yen in the case of after effects impediment grade 1. The amount of money for after effects impediment grade 2 in the later corresponds to grade 6 in the former, and compensation for persons with after effects impediment grade 7 or below in the former is dropped.

Actually, many parts of Japan's adverse drug reactions injured party compensation system have failed as a result of enactment of the Product Liability Act, and it is time to drastically revise the system again. It is wrong to bring such a system—one that, moreover, is a compensation system for adverse reactions to drugs sold on the market in large quantities, as mentioned above—into the compensation system for victims for drug development.

Table 4 Patient Subject Compensation Insurance

Clinical trial compensation liability insurance rider
- Death: 20 million yen
- After effects impediment
Grade 1: 70 million yen
Grade 2: 50 million yen

Compensation for Clinical Research Besides Chiken: "Ethical Guidelines on Clinical Research"

As mentioned at the beginning of the paper, ICG-GCP was introduced in Japan only for trials covered by the Pharmaceutical Affairs Act and, different from in the West, is not considered the standard for other clinical research. In July 2003, the Ministry of Health, Labour and Welfare finally created guidelines called Ethical Guidelines on Clinical Research, but subject protection is remarkably lacking compared to trials that have adopted ICH-GCP.

The Ethical Guidelines on Clinical Research were substantially revised in 2008. However, looking even at the description of the 2008 version, which is purported to have reinforced content, the regulatory authorities require for the first time the heads of clinical research organizations and others to "[purchase] insurance and take other necessary steps for compensation for health damage to subjects," but then at the same time they overturn with the own hands this principle set up at the beginning by expressing the opinion that compensation is not needed if it is explained to the subject and the subject gives consent that compensation is unnecessary. The biggest reason for this is that the real sponsor of "other research" is very often the national government, and it does not provide big enough grants to researchers for them to pay the insurance premiums.

The following explanation is from a consent and information sheet used by JCOG,*3 a research organization subsidized by the government:

"There is a possibility of developing unforeseen serious complications or other health damage during or after completion of participation in this clinical study. In that case, appropriate responses will be taken, the same as with treatment for health damage in usual medical care. However, the medical expenses shall be borne by the patient, since the treatment will be provided as health-care services provided under health insurance, the same as usual treatment.

*3 JCOG (Japan Clinical Oncology Group) is a research organization run partially with research funding of an Oncology Grant-in-Aid from the Ministry of Health, Labour and Welfare and partially with a Health and Labour Sciences Research Grant called a Grant for the Third-Term Comprehensive 10-Year Strategy for Cancer Control. It consists of 13 specialty study groups and enjoys the participation of nearly 200 hospitals across Japan.

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From left to right: Author, Dr. Wonchat Subhachaturas (Thailand) and Dr. Torunn Janbu (Norway)

If you feel some kind of health damage that does not occur during usual treatment, as a result of participation in this clinical study, inform your doctor without reservation. Also note that no sympathy money, other type of benefit, or any kind of special financial compensation has been prepared for health damage sustain in this clinical study."

As is evident from the above, it must be said that this just puts the burden on patients/subjects, who are in a weak position, and goes against the spirit of subject protection raised in the GCP, which is in the same spirit of the DoH.

Not until very recently did I hear that the regulatory authorities are recommending researchers to take out insurance. However, with people, including the regulatory authorities, unaware even of the distinction between liability insurance and compensation insurance, the reality in Japan is that compensation insurance in this field is undeveloped and researchers are not responding appropriately (whether or not negligent).

Table 1 is shown first to present this paper's conclusions. Once again, it is a list of whether or not there is compensation, and if there is, the content and degree of compensation, and whether or not it is backed by insurance and the kind of insurance, with respect to clinical research covered by the GCP ministerial ordinance and other clinical research (i.e. clinical research covered by the Ethical Guidelines on Clinical Research), out of clinical research that is subject to ICH-GCP. As I said at that time, the overwhelming majority in terms of number and types of research, out of all the clinical research conducted in Japan, falls within the right-hand column of "other clinical research." Everything is undeveloped in the current situation in Japan, requiring immediate improvement, including legislation.

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