Guideline for Proper Performance of Contract Services Proposed by the Japanese CRO Association (Revision 7)

General Incorporated
Japan CRO Association

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1. Background of Japanese CRO Association

The Japanese CRO Association (hereinafter referred to as "the Association") was founded on September 1, 1994 by CROs (abbreviation for contract research organizations, which provide services to perform part of duties and functions related to sponsoring and managing a clinical trial or post-marketing clinical trial of a drug transferred by a sponsor (hereinafter referred to as "Contract Services") in Japan, for the purpose of seeking the way CROs should be and promoting sound development of Contract Services in Japan.

The CRO was legally recognized as for the Organization of Contracting Research Activities under the new GCP, namely the Ministerial Ordinance of Good Clinical Practice for drugs as of effective in March, 1997, establishing the Guideline for Proper Performance of Contract Services by Japanese CRO Association in September of the same year, amending the 3rd version in August 2007. This was the 7th revision of the guideline due to the diversification of scope of contracting services in the business area such as medical products, medical devices, regenerative medical products, quasi-drugs, cosmetics, food products and the like; further the dramatic changes in contracting duties by the increase of multinational clinical trials, or the expansion of in-country caretakers' duties of clinical trials.

2. Purpose of Guideline

The Guideline stipulates the basic principles to continue the business activities by ensuring the reliabilities and quality of contracting services.

The Guidelines aim at increasing the clients' (prospective sponsor) reliabilities and developing by observing the Guideline by each Association Member and its further expansion and growth in the entire industry.

3. Observing the related regulations

In conducting Contract Services, the Members must observe all the applicable laws, rules, and regulations such as the Law for Ensuring Quality, Efficacy and Safety of Drugs and Medical Devices (commonly-called the Pharmaceutical and Medical Device Act), Clinical Research Law, GLP, GCP, GVP, GPSP and the like relating to medical products and devices, regenerative medical products. In addition, the Members' personnel must understand and be aware of those laws, rules and regulations.
The Members must also establish the standard operating procedures (hereinafter referred to as "SOPs") for all Contract Services to be conducted so as to attain the adequate quality assurance for their services, including observation of related laws, rules and regulations.

4. Scope of Contract Services

The Guideline stipulates the following Contract Services among services by the Members.

1) Research and development of medical products and devices, regenerative medical products
2) Regulatory affairs services of medical products and devices, regenerative medical products
3) Services following the marketing by manufacturers of medical products and devices
4) Research and development services for quasi drugs, food and cosmetics
5) Clinical research of medical products and devices, regenerative medical products
6) Any supporting services associating to the above-mentioned services No. 1 to 5. Also, the dispatching services of Members' associates could be included in the scope of services.

5. Evaluation of Appropriate Contracting

The Members should evaluate the appropriateness of contracting services, when they are in doubt in view of the ethical or the scientific points as needed.

6. Quality Control and Quality Assurance of Contract Services

The Member should perform and maintain the quality control activities and quality assurance based on the SOPs in order to observe the applicable laws and to ensure the appropriateness of whole processes and data reliability of Contracted Services, when conducting services.

Especially, in contract services relating to clinical trials, the Members should assure the quality of their Contract Services by means of Audit Activities (hereinafter as referred to as "Audit Activities") by independent organization from their operating divisions.
The Audit Activities should be conducted as part of quality assurance system of the Members, but not be replaced with Contract GCP audits requested by clients.

The Members should compile the SOP relating to conducting the audit activities and ensure that the audit should be performed in compliance with the SOP.

The Members should designate the auditor who shall meet the requirements to adequately perform the audit, independent from the operating Contracted Services.
The auditor should document the observations from the Audit Activities and compile the audit report for reporting. The Members should not in principle accept the blousing of audit reports by consigners and regulatory authorities to keep the independence of audit and credibility. The Members can submit an audit certificate to demonstrate the conducting of audit, when being requested by clients.

The Members should reference to "Guidance to Audit Activities by CRO (as of Feb. 1,

2011)" compiled by JCROA GCP Working Group.

The Members should also attain the quality assurance of Contract Services for Post-marketing services, voluntarily self-inspection (hereinafter as referred to as "Self-Inspection") as part of quality control and quality assurance system. The Self-Inspection should not be taken place with a self-inspection contracted by consigners. The person-in charge of Self-Inspection should be in principle independent from the subjected Contract Services, but not necessarily requesting its independence from their assigned organizations.

7. Indemnification and Compensation for Health Damage

The health damage indemnification is compensation for loss or damage despite of lawful behaviors, and compensation for damages is in principle to accept the liability for compensation from damages by negligence toward professionally required cautions.

1) Indemnification for Health Damage
The Members should ensure that the client (prospective sponsor) has purchased clinical trial insurance or taken other action to enable the client indemnify subjects for health damage prior to concluding a service agreement when they plan to conduct part of duties and functions related to monitoring in terms of managing a clinical trial transferred by the client.
Further, the Member should establish the procedures to compensate the expenses for treatment to health damage and/or other damage deriving from the Contract Services and should conduct duties in terms of compensation of health damage in accordance with the SOP in collaboration with the client.

2) Compensation for Damage
If the direct damage in the contracted services due to the negligence toward professionally required cautions by the Members are demonstrated, the Members might assume the the liability for compensation. In some cases, the lost profit will be included in the scope of claim for damage. However, in view of equal distribution of damage, the Members might exceed the limit of responsible amount of payment and endanger the business foundation, result in interfering with the sound development of CRO business area.
Therefore, it is desirable for the Members to stipulate the scope of compensation only limiting to direct damage, gross negligence as prerequisites and staying the compensation payment within the contracted gross amount in the contract with the clients in advance to starting the services as the responding countermeasures.
The following contract composing could be considered.

Article XX: Compensation for Damage

I. The client or CRO Members may claim for the loss caused by the negligence of duties stipulated in the contract or its violation. However, the claim should be limited to the ordinary or direct compensation for damage, the two parties shall not bare the compensation unless otherwise the intention and gross negligence.

II. In the preceding clause, the payment by CRO Members shall not exceed the amount

paid to CRO from the client by the time of negligence or contract violation on account of any reason.

It is desirable for the Member to purchase the CRO liability insurance policy that JCROA is the insurance contractor for the Member insured in preparation for payment obligation caused by indemnification for health damage or compensation for damage due to CRO Members faults and/or responsibilities.
If the Members contract to act as an in-country clinical trial caretaker, they should take a measure to indemnify or compensate in the same manner as the client should.

8. Training

The Members should provide their Staff engaged in Contract Services with training programs to allow the Staff to acquire knowledge and skills to properly perform Contract Services. They should designate responsible personnel for training.

The Members should stipulate the SOPs relating to the training. The training program should include the contents provided in the JCROA CRA Education and Training System General Rules and its detailed rules for personnel engaging to monitoring services.
The responsible personnel for training should make a training plan and implement in compliance with each SOP stipulated by the Members.
The responsible personnel for training and trainees should create and keep training records (e.g., time, date, duration, theme, and lecturer).

9. Monitoring

The requirements needed for monitors are clearly established in the Ministerial Ordinance on Good Clinical Practice (GCP) for Drugs since they visit the medical institutions and directly deal with the medical information of subjects.
The Members must provide their monitoring staff with training which enables them to perform monitoring services sufficiently and with GCP requirements, scientific and clinical knowledge required for the performance of the Contract Services in accordance with the SOPs for the Contract Services. They must designate monitors eligible to conduct the Contract Services.
They must train the selected monitors to have technical knowledge and information regarding the Contract Services and continuously provide their monitoring staff with training. Monitors should ensure that the rights, safety and welfare of subjects are well protected in the clinical trial and that the clinical trial is conducted in compliance with applicable laws such as the GCP and the protocol. They should also confirm that data from the clinical trial reported by investigators and sub-investigators are accurate by comparing them to source documents and other records related to the clinical trial in compliance with Article 21; Monitoring and Article 22; Monitor’s Responsibilities in GCP Ordinance, respectively.

10. Compliance

The Members should execute the contract services based on contracts with sponsors, however, prioritize not only the conformity to laws and regulations relating with medical products in GXPs and medical devices, regenerative medical products, but always take precedence the safety of subjects and ethical codes and have a great responsibility in accelerating standards and improvements for clinical processes. In addition, the members should endeavor to continue the internal training and fostering the corporate climate aiming at maintaining the higher bioethical view.
The Members should respect and work cooperatively the practice for transparent relation between the pharmaceutical companies and medical institutions and reject any requests against this practice.
The Members should not give the bribery or propose and promise illicit interests to personnel belonging to government, local public agency, National Hospital Organizations and sanatorium.

11. Information Security

The Member should conclude the secrecy agreement with the client when receiving the material, data and information (hereinafter collectively referred to as "Information" regardless of tangible or intangible) related to Contract Services from the Client. They should be strictly responsible for storing the secrecy information obtained by conducting Contract Services.

The Member should secure the information security by taking appropriate measures protecting from misconduct and/or injustice to the Information (e.g. data disclosure, destruction, falsification, illegal access and taking out the equipment and/or instrument and so on) including the personal information.

The Member should also take the back-up measures against such risks as natural disaster (earthquake, seismic surges or TSUNAMI), fire, system failure (equipment default, software error, and network failure). Also, they should minimize the impacts from the failures, rapid recovery and take steps for cause investigation and protection of recurrence.

12. Response to Critical Situation

If a Member runs into a critical situation which may disturb the conduct of Contract Services, the Association should give top priority to protection of the rights of subjects involved in the Contract Services, and should collaborate to select a successor of the Contract Services within the Association if requested by the client. The contractee who has succeeded to the Contract Services should conclude a separate agreement with the client to conduct the services.

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