GCP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 1：QMS**
Subgroup	**C-1-A**
Theme	**The Clinical Trial: How to Guarantee "Quality"** – Clinical Trial QMS as Envisaged by JSQA, and its Execution –

Study Group 1 Subgroup A ("our Group") commenced activities relating to our Group's theme, "The Clinical Trial: How to Guarantee 'Quality' – Clinical Trial QMS as Envisaged by JSQA, and its Execution –," with the aim of producing deliverables which would useful for the implementation of QMS in clinical trials from a practical perspective.

In May 2016, when our Group's activities began, agreement on the ICH-E6 (R2) Step 4 was to take place by the end of the year, and industry groups were engaged in discussions and study sessions based on ICH-E6(R2) Step 2. Likewise, the majority of our Group members wished to understand the "key points" necessary for QMS implementation stipulated in ICH-E6(R2) ADDENDUM as compared to the clinical trial QC/QA stipulated in the then current ICH-E6(R1). On the basis of these needs, our Group chose to focus on investigating matters which would be useful for implementation of individual elements of QMS, instead of risk management or CAPA methodologies. Our Group formed two teams and formulated deliverables from the following perspectives.

1) Team focusing on items in analyzing QMS stipulated in ICH-E6(R2) ADDENDUM

Out of items added as ICH-E6(R2) ADDENDUM, our team focused on risk management. We investigated 5.0 Quality Management, an item believed to be an important element for clinical trial QMS. Item 5.0 calls for implementation of quality management taking a risk-based approach. Albeit in varying degrees, none of the companies appeared to have established a fully satisfactory QMS. Therefore, the team prepared an overview of each item and a Q&A of possible questions, so that companies could put them to use in building and implementing QMS with a risk-based approach.

2) Team investigating the framework and components of QMS

In regard to clinical trial QMS, we are now seeing a full array of structures preparing for the shift from exit management to process management, including risk-based monitoring, which is one of the targeted directions of QMS. ICH-E6 (R2) has also served as an impetus for vigorous debate by industry groups regarding their approach to QMS framework/components such as risk management, knowledge management, and issue management. Therefore, our team focused on issue management out of the clinical trial QMS framework/components, and investigated the items which were added in the ICH-E6 (R2) ADDENDUM. We divided issue management into 8 processes and presented "ideal" samples of each process, so that they might be of use when implementing issue management.

Out of the QMS elements stipulated in ICH-E6 (R2) ADDENDUM, our Group focused on risk management and issue management to formulate our deliverables, which we believe should be of service when considering clinical trial QMS from a practical perspective. We hope our deliverables, with adjustments made as necessary, will be of use to member companies.

GCP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 1：QMS**
Subgroup	**C-1-B**
Theme	**Clinical Trial Quality Management Systems (QMS) Expected of CROs**

Our Group deliberated on, and prepared, a “Guidance for Establishment of QMS” which would be of use to CRO divisions involved in clinical trials when establishing a quality management system (“QMS”). Our investigation also aimed, as much as possible, to present useful tools for QMS operation. We also collected information on problematic cases arising from discrepancies in understanding between sponsor and CRO, and explored solutions from a QMS perspective. In our investigation of QMS, we referenced the requirements in the ICH E6 guideline revision and ISO9001:2015.

Our deliverables for this term were as follows:

1) Guidance for Establishment of QMS

This Guidance was based on QMS establishment in organizational units (e.g. clinical development division) and had as its main components, “quality policy,” “quality objectives,” “procedures/protocol,” “execution,” “evaluation,” and “improvement.” It was structured so that the operations in each contracted assignment would be carried out according to the QMS of the organizational unit, and their output would lead to the organizational unit’s “evaluation” and “improvement.” QMS management items were set as “management by objectives,” “risk management,” “issue management,” “resource management,” “competence management,” “communication management,” and “change management.” The procedures and key points for each item were shown in the guidance, with a management table prepared for each item except resource management, together with sample entries or key points.

2) Case studies of discrepancy issues

The Group collected discrepancy cases from member companies. These were cases in which the sponsor or CRO felt a discrepancy at any stage from preparation of the clinical trial to compliance inspection, on the premise that they relate to monitoring. Past deliverables by JSQA GCP Division were also referenced. The cases were investigated by “root cause analysis,” “impact,” and “measures,” and summarized in a list. Consideration of the discrepancies which may arise between sponsor and CRO is important in the appropriate establishment and operation of QMS as well as for establishing a partnership between sponsor and CRO, and we believe our case studies will be of use.

We hope our deliverables will be useful when establishing and operating QMS according to company policy at each CRO. By doing so, it should be possible to achieve goals and continuously improve quality in the organization, leading to sustaining and enhancing the value of the CRO itself.

GCP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 1：QMS**
Subgroup	**C-1-D**
Theme	**Q&A for Clinical Trials for Medical Devices**

In response to the enforcement of the Ordinance Concerning the Standards for Clinical Trials on Medical Devices (2005 MHLW Ordinance No. 36), a group for investigating clinical trials for medical devices ("medical device clinical trials") was set up for Term 8 (2006-2007) by the JSQA GCP Division. From the outset, our group continued to investigate medical device clinical trial QC/QA. In the previous term, our group performed risk analysis of medical device clinical trials and deliberated on how to improve their quality.

This term, we were mindful of the possibility of having overlooked questionable matters in previous deliberations. We therefore identified such matters and their solutions, as well as solutions to questions which persons familiar with pharmaceutical GCP might have in regard to medical device clinical trials, and differences between pharmaceutical and medical device GCP. We summarized these into a "Q&A."

In formulating the Q&A, we collected questions through our group members. However, the questions did not cover all of the categories of medical device clinical trials. Therefore, our Q&A pertains to "trial preparation" and "trial management."

As an aside, immediately prior to the completion of our deliverable, the Japan Federation of Medical Devices Associations, Clinical Evaluations Committee issued the "Guidance for Withdrawal of Consent in Medical Device Clinical Trials" (1st Ed., January 1, 2018), enabling us to formulate "A" in "Q&A 1.9 Protocol etc. (3)" on the basis of the Guidance. We believe this will assist in the broad dissemination of information on the Guidance.

GCP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 2：Audit**
Subgroup	**C-2-A**
Theme	**Aiming at Effective and Efficient GCP Auditing by Introducing the Concept of ICH Q8 and Q9** − Significance of Introduction, and Proposal for Actual Introduction Part 3 −

Purpose

In Terms 11 and 12, we investigated whether it is possible to adopt auditing methods to which the concepts in the "ICH guideline Q8: Pharmaceutical Development" and "ICH guideline Q9: Quality Risk Management" issued by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) are applied. Our investigation revealed the critical process parameters (CPP) of each of the two processes we looked into, and our results suggested that focusing on these CPPs would make it possible to implement audits effectively and efficiently, and to make proposals for appropriate corrective and preventative actions for the continuous improvement and maintenance of the quality system.

However, up to the previous Term, a great amount of time was required to analyze PMDA GCP compliance inspection findings ("findings") in order to identify CPPs. We therefore needed a more efficient process. Meanwhile, the CPPs obtained from the analysis of findings were believed to be the same as the CPPs conceptualized through the experience of auditors. Therefore, if the two CPPs can be shown to match, there would be no need to analyze the findings. Based on this approach, this Term we investigated whether there was a match between the two CPPs.

Method

1. Out of the "clinical trial processes" of Terms 11 and 12, we selected the "investigational drug administration" and "obtaining informed consent" processes.
2. We divided these processes into several sub-processes.
3. Based on the experience of auditors, we identified the harms in each sub-process, the process parameters (PPs), and the details of PP deviations.
4. Based on the experience of auditors, we identified the CPPs of each sub-process.
5. We analyzed findings and identified CPPs.
6. We compared the results of 4. and 5. above.

Results

・In the "investigational drug administration" process, there was a match between the CPPs based on the experience of auditors and the CPPs obtained from findings.

・In the "obtaining informed consent" process, there were sub-processes in which the CPPs based on the experience of auditors and the CPPs obtained from findings did not match.

・The reason for the mismatch was that the harms in the findings, which should have been included in the harms established by auditors, had been established as new harms. On the basis of the approach at the time of the investigation, the harms established by auditors and the newly established harms could have been construed to be identical. Therefore, we believe the two can be described as being the same.

Conclusion

An intrinsic consistency was observed between the CPPs based on the experience of auditors and the CPPs obtained from analysis of findings. Therefore, it was suggested that evaluation focusing mainly on CPPs based on the experience of auditors would make it possible to carry out audits

effectively and efficiently.

Other

As per the plan at the beginning of the Term, we summarized the results of our Term 11 and 12 deliberations and submitted them to the journal of the Japanese Society of Clinical Pharmacology and Therapeutics.

Title: “Proposal of Quality Management in Clinical Trials based on the Concept of ICH Guidline Q8” Jpn J Clin Pharmacol Ther 2018; 49(1):15 - 21

GCP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 2: Audit**
Subgroup	**C-2-B**
Theme	**Risk-Based Approach for GCP Audit**

[Introduction]

Subgroup B, Study Group 2 (“our group”) deliberated on the theme of “Risk-based approach for GCP audit” in consideration of recent changing situations in clinical trials. Past study group sessions of JSQA had discussed some conceptual themes about “quality management system in clinical trials” and “introducing risk based approach into clinical trials”. However, not enough discussions have yet been held about how we should handle “timing”, “target” and “method and how to assess the result of Audit in an effective way”. These are necessary to detect and analyze potential harms and hazards that may occur during clinical trials, and these enable a risk-based approach for GCP audit. Hence, the activity which came from “investigation of auditing techniques which incorporate risk-based approach” in previous period (No. 15C11), was taken up by our group. So, we would suggest an audit plan model that applies the measures for risk reduction, designing that a transition from conventional “Retrospective QA” to “Pro-active QA” in the group activity.

[Methods]

All members of our group brought issues regarding risk assessment. The issues have information related to 15 points~~,~~ such as “target system,” “breached GCP articles,” “frequency of audit,” “target person,” “contents of the issue,” and “how the issue was found”, etcetera. We classified the issues with “GCP article” and “The category*,” and tallied up the issues focusing on 8 items such as “target system,” “category,” “GCP article”, etcetera. In addition, we carried out risk evaluation using preset conditions, such as “severity level,” “frequency level,” “risk level. We considered and formulated the plan for risk reduction applying the visualized result of “classification”, “counting” and “risk evaluation.” Whenever necessary, we revised the adequacy of “classification”, “counting” and “risk evaluation” in our group meetings.

[Results]

Totally, ninety issues were collected within our group, which each member had discovered under several conditions. We conducted risk evaluation and then decided the risk level of these issues. We succeeded in identifying issues which have a tendency of high risk level and decided the target of audit by using the visualized evaluation result with trend analysis. Also, we clarified points of attention in audit through revising an audit strategy, identifying a requisite audit target on the basis of both the measures for risk reduction of investigator site audit on a previous site and those of a current system audit/investigator site, and revised the frequency of audits. Herewith, we propose the effective and efficient model of “tactical audit plan,” “system audit plan,” and “investigator site audit plan.”

[Discussion]

For the record, it is a hypothetical suggestion that we have shown in this article, because we conducted the risk assessment with simulated data for a better understanding of risk management methods. However, it is critically useful in risk based approach that we drew up a “tactical audit plan,” “system audit plan,” and “investigator site audit plan.” And we believe that these are plans which can extrapolate into risk based quality management in ICH-GCP (R2) for finding the suitable risk based approach. The right approach is an important thing in understanding risk based quality management system. We really hope that this article is better used for consideration of the measure for risk reduction and system building for quality management in your esteemed organization.

* This is an arbitrarily defined content because of making trend analysis easier.

GCP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 2：Audit**
Subgroup	**C-2-C**
Theme	**The Concept of GCP Audit for Risk-based (as Broadly Defined) Monitoring**

In recent years, sponsor are adopting a risk-based approach (RBA) to quality management for the purpose of effective and efficient assurance of clinical trial reliability (accuracy of data, scientific validity of the trial, protection of the safety and human rights of trial subjects). New tools are being adopted which monitoring execution status on the basis of predicted risks (risk-based monitoring, RBM).

Clinical trials involve various processes which differ from those of general practice, and there are potential risks in each process. In a clinical trial with RBM, identifying and considering those risks appropriately in managing the trial is expected to take on even greater importance.

In Term 13, the Group C, Study Group 2, GCP Division looked into the specific tools used by GCP auditor when evaluating the quality control status of clinical trials using RBM. We summarized new auditing perspectives and key points for the appropriate evaluation of clinical trial quality on the basis of ICH E6 (R2), and prepared an Audit Guidance.

We separated our group into two subgroups to analyze the issues under either “clinical trial site audit” or “system audit.” Thus the Audit Guidance is divided into two parts.

At the 17th Conference on CRC and Clinical Trials 2017 in Nagoya, held in September 2017, we gave a poster presentation on the approach and overview of the audits we investigated. Our presentation was met with a high level of interest from participants.

We believe our Guidance will serve as an aid in considering quality assurance, not only for GCP auditors but also for all parties engaging in data quality management.

It should be noted that the content of the Audit Guidance represents a certain perspective based on the results of deliberations by our group on the basis of information available at this point in time.

GCP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 2：Audit**
Subgroup	**C-2- D**
Theme	**Group Audit of Contract Research Organizations**

Since it became possible to contract all of the operations relating to carrying out and managing the clinical trial, the sponsor's audit of the contract research organization (CRO) has played an important role. Both auditor and auditee routinely perform many auditing and related activities to assure reliability.

Out of audits performed on CROs, there is little inter-sponsor difference in the system audit, which is the core of the audit. In light of this current situation, we considered an efficiency-improving scheme in which multiple companies come together to perform audits as a group (group audit). We carried out the following three group audits: (1) System vendor; (2) Clinical laboratory; (3) Clinical trial support system operated by the Japan Medical Association Center for Clinical Trials. In our present investigation, we commissioned the group audits of (1) and (2) above to an outside audit service company. In our scheme, companies participating in the group audits were not subjected to a direct audit. For (3), audit was performed by members of Study Group 2 Subgroup D.

1. System vendor: Fujitsu Limited (DDworks21)

Auditing of system vendors requires a high level of expertise, and there is concern as to whether audits are being carried out satisfactorily. Furthermore, outsourcing is hampered by the high costs involved in commissioning such audits to outside experts. It is also likely that frequent visits by auditors are a burden on the system vendors receiving the audits. Our group audit demonstrated that group audits are an effective means for resolving audit-related issues such as CSV audits, which require a high level of expertise and are expensive when performed alone. Group audits are also in high demand by companies. Even so, the issues relating to contracts and other matters revealed in our investigation indicate that further deliberation is necessary for the smooth implementation of group audits.

2. Laboratory testing services company: BML, Inc.

Audits of companies which provide laboratory testing services are usually carried out individually by each company using their own internal resources. Despite our initial concern of whether we needed to offer additional benefits in order to have companies willing to participate in a group audit, we in fact had more than 10 companies respond to our call. Out of the reasons for participation, the one chosen by the highest number of companies was, surprisingly, that they did not have enough expertise. Our audit was meaningful in that it gave companies affordable access to audit results by an audit service company with a high level of expertise. Another suggested benefit was that the participating companies could exchange views with one another, a feature made possible by the group audit format.

3. Clinical trial system operator: Japan Medical Association Center for Clinical Trials ($CtDoS^2$)

This audit of a clinical trial system operator was conducted as a participatory group audit implemented by a member of Study Group 2 Subgroup D. Participatory group audits offer benefits which include improvement of mutual knowledge through information-sharing by participants, more standization of audit details or criteria, a more extensive audit in a shorter time, ease of incorporating participant-specific parameters, and low commissioning cost. Our group audit revealed that, compared to group audits commissioned to outside experts, there were benefits including more standardization of audit criteria due to advance consultation by all parties, a more extensive audit in a short time, and reduced cost.

GCP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 3: Electronic**
Subgroup	**C-3-A**
Theme	**Investigation of eTMF and CDISC Standards**

Team 1

Subgroup A Team 1 focused on "consideration of eTMF systems."

We first shared information on eTMF and performed eTMF inspection case studies to investigate the need for eTMF systems. At the same time, we identified issues relating to eTMF systems, examined those issues, and finally investigated the two themes of process management using eTMF systems and approaches to establishment and management of eTMF systems.

During the information-sharing and case studies, we looked into TMF (definition and history), eTMF systems (current situation, degree of necessity, what to consider before adoption), and the situation around eTMF (regulatory trends in Japan and overseas, FDA and EMA inspection case studies, multi regional clinical trials). On the basis of these investigation results we believed that eTMF systems were necessary.

In the subsequent issue identification and examination of eTMF systems, we ultimately compiled "eTMF Process Management" and "Approaches to Establishment and Management of eTMF Systems." In the former (eTMF Process Management), we indicated that eTMF contained elements (metrics, RBA, etc.) for process management and was likely to help reinforce inspection readiness, etc. Furthermore, we demonstrated the utility of eTMF systems by proposing procedures for process management (PDCA) corresponding to QMS defined in ICH-GCP E6(R2) expected when utilizing an eTMF system. In addition, we revealed issues for the future. In the latter (Approaches to Establishment and Management of eTMF Systems), we gave examples of various key points requiring consideration, such as gaining internal consensus in relation to adopting an eTMF system. Furthermore, we presented an efficient, comprehensive list of key points which should be of use to companies starting to consider adoption of eTMF systems.

Team 2

Subgroup A Team 2 built on the previous term's activities and focused on "QC/QA in the context of CDISC standardization." We delved further into the results of the previous term and prepared deliverables which mention the key points requiring attention in creating electronic data etc. in each step from protocol formulation to preparation of the clinical study report, taking CDISC standardization into consideration.

On the basis of GCP, we identified the processes likely to require QC and QA, and incorporated these into a flow chart.

We also indicated key points for system audits and audits of individual clinical trials to verify that items relating to electronic data for submission are compliant with CDISC standards.

We recommended that companies create internal standards which consolidate preparation processes of electronic data for submission and perform system audit to reduce the burden of performing audits for each trial. We also proposed that, while it is advisable that a complete array of internal standards be prepared, there needed to be such standards for SDTM and ADaM at the minimum. We also proposed that preparation procedures of electronic data for submission which are not internally standardized should be subjected to audit for each trial in accordance to the data management plan or other procedural manual prepared for each trial.

We recommended that, although it is acceptable to perform QA all at once prior to preparation of the CSR, it is preferable that it be carried out in four parts, each timed as follows: immediately after protocol formulation; after database lock; after finalization of analysis results; and after preparation of the Reviewer's Guide.

GCP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 3: Electronic**
Subgroup	**C-3-B**
Theme	**EDC System Integration**

Our group conducted a survey and investigation into EDC system integration, particularly the integration of electronic medical records (EMR) and EDC data.

With the recent groundswell of big data utilization in medicine, we can expect more movement toward the long-awaited, yet still not widely adopted, integration of EMR and EDC. In fact, our survey revealed the emergence of several cases which are at the level of verification testing or practical use.

There are various potential formats for entering EMR data into EDC. We organized, into three categories, the formats which have either been used successfully to date or are being considered for use going forward: “intermediate data transfer,” “SS-MIX,” and “data request.” From the standpoint of clinical trial data quality, we summarized the advantages of each format, and the criteria for their realization.

Overall, each format has strengths and weaknesses and it is not possible to make a judgment as to which method is the most advantageous. However, in terms of improved data reliability and quality, we believe any of the methods would be beneficial both for the sponsor and the clinical trial site.

Meanwhile, within the scope of our survey which we conducted to identify the current situation, we found that there was still no “permanent” EMR/EDC integration service capable of handling a wide variety of clinical trial protocols in multiple clinical trial sites, remaining at the level of research-based verification testing.

In the context of rising interest in medical big data and real-world data, and expectations for the secondary use of EMR data, we believe there will be a need to present a comprehensive picture for the future, which goes beyond the scope covered in our activities and includes the collection and utilization of medical big data and real-world data.

GCP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 3: Electronic**
Subgroup	**C-3-C**
Theme	**What is WHODrug?** - From Adoption to Applying for Electronic Submission of Study Data for New Drug Applications-

Submission of electronic clinical trial data when applying for approval began in October 2016 and will be made mandatory in 2020. The PMDA's "Notification on Practical Operations of Electronic Study Data Submissions" (PFSB/ELD Notification 0427-1, April 27, 2015) requires the use of CDISC standards and coding of drug names according to WHODrug.

WHODrug is not well known. This is particularly the case with Japanese companies, few of which have experience with it. Therefore, information is lacking on its introduction or its coding system, let alone its coding methods. A compounding factor is that the documents and seminars offered by UMC are mainly designed for subscribed users. As things currently stand, there is not almost opportunity to obtain the information before subscribing.

Using various documents prepared by Uppsala Monitoring Centre (UMC) and information from User Group Meetings as a guide, our group prepared informational material containing information on WHODrug adoption, types of dictionaries, coding system, coding methods, information outside Drug Code and ATC, and a summary of key points for use. Our material focuses mainly on the WHODrug Global B3/C3 format and is designed for members considering the adoption of WHODrug. To address the needs of members already using WHODrug, we explain the changes from the B2/C format and points requiring attention.

WHODrug is continuously updated and undergoes revisions on a regular basis. Even during our activities, there was a major change in the dictionary type and coding system. In this change, all dictionaries were combined as WHODrug Global and UMC accomplished the unification of the coding system including the combination drug which was a longtime desire. Though no major changes are planned for the time being, this process of constant change is expected to continue, both with WHODrug and with regulatory authorities. We recommend that users of our informational material constantly obtain the most up-to-date information from UMC, CDISC, PMDA, etc.

Lastly, it should be noted that WHODrug is nothing more than a dictionary of drug names, and the crucial key to its utilization will be why and how the users use the system. As long as those matters are made clear, we believe companies will be able to find ways to use it appropriately in accordance with their individual situations, taking into consideration the characteristics of WHODrug.

GCP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 3: Electronic**
Subgroup	**C-3-D**
Theme	**The Use of IWRS in Investigational Product Management** - Adoption Process and Utilization Status -

Following the revision of the GCP Ordinance in 2008, it became possible to supply investigational product through third parties such as delivery companies. Utilization of outside warehouses and delivery services is now commonplace. In recent years, the use of interactive web response systems (IWRS) is also on the rise, with the objective of efficient implementation and management of the clinical trial.

In light of this situation, our group chose “Investigation of Methods for IWRS Adoption (Establishment and Operation) Focusing on Investigational Product Management” as our theme, for the purpose of creating a guide for IWRS adoption designed for sponsors with no experience with IWRS.

IWRS is built for each clinical trial in accordance with the trial protocol and has functionalities for subject enrollment and investigational product management, out of which the subject enrollment function is in wide use. Investigational product management functions include “management of trial site inventory of investigational product,” “instructions to supply investigational product according to site inventory,” and “emergency key code management.” The particulars of the functions differ by vendor. The sponsor selects the necessary functions on the basis of trial protocol, and works with the vendor to finalize the IWRS specifications.

One of the characteristics of IWRS use is its access by both sponsor and site staff (investigator, CRC, etc.).

Our group examined questionnaire responses from sponsors regarding their experience with IWRS, to summarize a status report on IWRS use by sponsors (reason(s) for use/non-use of IWRS, background of trial(s) involving IWRS use, etc.). We also considered key points and adoption processes (timeline required for IWRS adoption, information to provide vendors, etc.) using the results of both interviews with IWRS vendors and a survey of sponsors.

We hope our results will be of service to IWRS users and to sponsors considering the adoption of IWRS.

GCP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 4：Field**
Subgroup	**C-4-A**
Theme	**Investigation of the Issues Relating to Clinical Trial Quality Assurance in Light of the Realities of Medical Institutions** (Communicating and Disseminating the Essence, Concepts, and Actual Initiatives for Quality Assurance of Clinical Studies and Data; Resolving the Issues of the Medical Institution; etc.)

Quality assurance in clinical trials has been explored and promoted by various organizations, companies, and medical institutions. As of 2016, when Term 13 of JSQA activities were to begin, there were numerous clinical trials in Japan which required further improvement in terms of quality. In addition to the fact that the predecessor of our group had been investigating the principles of ALCOA (-CCEA) up to the previous term, the tide of risk-based approach/monitoring due to the recent revision of ICH-E6 (R2) was already imminent. In response, our group embarked on an investigation of the following two themes for Term 13, keeping in mind the realities of medical institutions.

1) Efforts to resolve clinical trial site issues relating to ALCOA-CCEA compliant source document management (ALCOA team)

The ALCOA team conducted investigations and prepared documents to make proposals relating to on-site ALCOA-CCEA compliant source document management. Firstly, we aimed to collect information on the attitudes and realities of medical institutions in relation to ALCOA-CCEA through a questionnaire of CRC personnel who are members of Japan Association of Site Management Organizations, Strategic Management and Operation Network Association for Clinical Study, or a medical institution. We received 790 responses. This “feedback from the front lines” suggested that the importance of “identification of source documents” and “documentation of internal procedures” was recognized, and ALCOA-CCEA compliant quality assurance was being implemented. Meanwhile, the issue of difficulties stemming from inter-sponsor differences in ALCOA-CCEA requirement levels had yet to be resolved. We presented some of our questionnaire results at the 17th Conference on CRC and Clinical Trials 2017 in Nagoya. In addition, on the basis of our questionnaire results, we prepared a “Source Document Management Checklist” to be of use in promoting ALCOA-CCEA compliant source document management, and “ALCOA-CCEA Cards” which can be carried around by hospital staff.

2) Efforts to assist clinical trial sites in the resolution of issues and avoidance of risks relating to new risk-based approach/monitoring initiatives (RBA team)

The RBA team aimed to create materials for medical institutions to use when adopting RBA/RBM, so that they can alert themselves to risks and reduce them. To that end, there was first a need to get all participants in the investigation onto the same page in regard to RBA/RBM. This required a considerable amount of time, but we succeeded in giving all participants a shared perspective in subsequent investigations and considerations, although not a few differences were revealed in the degree of understanding, progress, and stance regarding RBA/RBM between companies and organizations to which participants were affiliated. We then categorized risks, collected cases, and summarized from the numerous pieces of information the following nine processes which require particular attention on the part of clinical trial sites when implementing the trial: (1) Explanation of the trial and obtaining informed consent, (2) Verification of subject

eligibility, subject enrollment, and allocation, (3) Investigational product, (4) Laboratory tests, (5) Obtaining consent to continue the trial (re-consent), (6) Occurrence of AE/SAE, (7) Occurrence of deviation, (8) Preparation of source documents and case report forms, and (9) Discontinuation/completion of trial.During our investigation, we held meetings with CRCs of external medical institutions to exchange views and gain feedback. Ultimately, we summarized case-specific flow charts and rksks and risk reduction measures for all nine processes, and created “Risk-based Quality Management Toward Implementation of Risk Based Approach (RBA) in Medical Institutions” which can be put to use in institutional self-assessments and staff education.

The deliverables prepared by our two teams are scheduled to be released on the JSQA public website.

GCP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 4：Field**
Subgroup	**C-4- B**
Theme	**An Examination of the Future of Quality Assurance of Investigator-initiated Clinical Trials (for NDA) and Clinical Research (for EBM), and an Information Center for Inquiries from Outside of JSQA Relating to Quality of Investigator-initiated Trials and Clinical Research (Q&A creation, etc.)**

For six years from the two previous terms, Subgroup B of Study Group 4 has worked on the issue of quality assurance in investigator-initiated clinical trials for NDA ("CT") and clinical research for EBM ("CR"). Up to the previous term, we investigated "QA/QC in CT and CR," comparing and assessing the differences in regulations in Company-sponsored Clinical Trials for NDA, CT and CR, and investigating monitoring/auditing cases and questions relating to CT and CR. We also prepared QA/QC checklists for CT and CR respectively, with cooperation from JSQA non-members working at research institutions. The checklists have already been made public on the JSQA website as our deliverables.

This term, we mainly focused on audits which are the means to assure quality in CT and CR. We prepared the following deliverables for first-time audit recipients, covering specific concepts and methods of auditing CT and CR respectively. The following deliverables have been made public on the JSQA website.

・CT Audit Manual
・CR Audit Procedures
・CR Audit Procedure Guide
・CR Audit Manual

We hope these deliverables will be an aid in assuring reliability in CT and CR.

It should be noted that the Clinical Research Act was promulgated (April 14, 2017) during this term, and there is higher awareness in society in regard to CR quality assurance. Since no Guidance to the Clinical Research Act was issued during our activities, we have limited the scope of our investigation of CR audit methods to those with the Ethical Guideline for Medical and Health Research involving Human Subjects as the prescribed documents. Going forward, in the event of issuance of a Guidance relating to the Clinical Research Act, there will be a need to update the Audit Procedures, Audit Procedure Guide, and Audit Manual to take the provisions of the Clinical Research Act into consideration.

Our other theme was to explore an "Information center for inquiries from outside JSQA relating to quality of CT and CR (Q&A creation, etc.)." We considered the establishment of a permanently maintained information center system with a view to collaborating with outside organizations. However, due to limitations on system-building beyond the term of our Study Group activities, we decided to concentrate on the aforementioned "CT Audit Manual" with the hope that the establishment of an information center system will be incorporated into the planning stage of projects scheduled for the next and subsequent terms.

GCP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Special Project Group 1**
Subgroup	**C-T-1**
Theme	**Examination of Case Examples of Compliance Reviews/Inspections**

Special Project Group 1 collected, examined, and analyzed 126 PMDA compliance reviews from Japan and overseas contributed by members of the JSQA GCP Division, and some case examples of compliance reviews obtained from PMDA by using the Law Concerning Access to Information Held by Administrative Organs. We also collected and examined the case example of an inspection by an overseas regulatory authority reported from member, as well as relevant regulatory information mainly from public sources. We presented our results as feedback to JSQA members at the annual "What's Quality & Compliance? – Review Meeting on Case Examples of Compliance Reviews/Inspections –."

1）Conferences

（1）What's Quality & Compliance? – Review Meeting on Case Examples of Compliance Reviews/Inspections –

・37th Meeting: March 24, 2017, Nissho Hall, Tokyo (attendance: approx. 650)
- Case examples of compliance reviews by PMDA (including the results of deliberations by Special Project Group 1 and introduction of Root Cause Analisys)
- PMDA special lecture: Introduction and future operation of PMDA GCP management sheet
- Trends in inspections by overseas regulatory authorities (including presentation by Special Project Group 5 on GCP inspections by regulatory authorities in China and South Korea)

・38th Meeting: March 9, 2018, Nissho Hall, Tokyo (attendance: approx. 650)
- Trends in inspections by overseas regulatory authorities
- Invited lecture: Experience with US FDA inspection in Japan – 6 sites, 1 CRO and 1 Sponsor inspection
- Case examples of compliance reviews by PMDA (including the results of deliberations by Special Project Group 1 and introduction of Quality Management System)
- Panel discussion on Risk Based Approach in clinical trials

（2）Website-based basic course

To give persons inexperienced with PMDA GCP inspections a better understanding at the Review Meeting on Case Examples of Compliance Reviews/Inspections, we developed a basic course offering information on compliance reviews, and made it accessible year-round on the JSQA website.

2）Deliverables

- Summary of deliberation results (37th and 36th Meetings) [distributed to Meeting participants and to companies which contributed case examples]
- GCP compliance review reports (37th and 38th Meetings) [distributed to Meeting participants (GCP Division members only) and to companies which contributed case examples]
- Data Listing of case examples of compliance reviews collected using the Law Concerning Access to Information Held by Administrative Organs [released on the JSQA website]

GCP Division, Activity Summary of the 13th Term (April 2016 – March 2018)	
Study Group	**Special Project Group 2**
Subgroup	**C-T-2**
Theme	**The Planning, Development, and Implementation of GCP Training Courses for Personnel in Charge of Clinical Trials**

We held 6 types of GCP training courses for personnel in charge of clinical trials. The courses ran for a total of 8 sessions over a term of 2 years.
The GCP training courses were designed to provide knowledge necessary for the process of clinical trial quality control and quality assurance, and to improve the skills of participants. The courses successfully achieved their purpose.
Through the participation in course development, the members of Special Project Group 2 were able to deepen their knowledge and understanding of GCP quality control, audits, and quality assurance, and resulted in upgrade their own skills.
From 2017, in parallel with preparations of the conventional courses, we also began discussing the entire training course program from a medium- to long-term perspective. We will continue to review of the courses the next term.
In this term, Special Project Group 2 members met once monthly in general for a total of 29 meetings for the purpose of course development.

Thefollowings are overviews of courses which we conducted.

QC/QA Beginners' Course (Offered twice: July 2016 and July 2017)
One-day course, Participants: 79 people in July 2016 and 70 people in July 2017
This course was offered to new staff of clinical trial operations and to those who wished to check on the basics. Designed to give participants a basic knowledge of QC/QA in the GCP area, the course consisted of lectures in "Overview of the Pharmaceutical Affairs Law and GCP", "Features and practicalities of clinical trials for medical device" "Overview of QC/QA" and a "Q&A Session."

QC Advanced Course (Offered once: November 2016)
One-day course, Participants: 33 people
This course was offered to persons who had work experiences of GCP quality control or monitoring (Participants were expected to be able to participate in the discussion based on their own quality control experience). The course mainly featured group discussions which had case studies and exchanges opinions based on the quality control experiences of each participant.

QC Basic Course (Offered once: December 2016)
One-day course, Participants: 34 people
This course was offered to persons with 1 to 3 years of experience in GCP QC or monitoring operations. The sessions featured a lecture titled "Practice and Overview of Quality Control" plus group discussions of case study exercises.

QA Basic Course (Offered twice: December 2016 and February 2018)
One-day course, Participants: 47 people in December 2016 and 54 people in February 2018
This course was offered to persons with less than 3 years' experience in GCP audit operations, and consisted mostly of classroom-style learning of "Introduction to GCP audit," "Case study exercises," "Introduction to GCP audit operations in actual companies (personnel from 2

companies introduced their respective firms' positioning of the audit division and the practical work of auditing)," and "Panel discussion" for first session. For second sessions, instead of "Introduction to GCP audit operations in actual companies" more detailed process of GCP audit process from planning to repoting of audit report was included.

Investigator Site audit Practical Course (Offered once: February 2017)
Two-day course, Participants: 21 people
This course consisted mainly of group work (role-playing) about a mock audit of a clinical trial sites, and was offered for the purpose of acquiring and/or upgrading the skills necessary for auditing clinical trial sites.Through review of essential documents and source data, and interview with site staff, participant learned how to proceed with auditing and the process of identification of findings and also they realized that there were various viewpoints and ways of thinking from group discussion.
It was a feature that participants were able to do interviews with real medical institution personell with clinical trial experience with the cooperation of Hamamatsu Medical University.

Basic Training Course for Quality of Clinical Study (Offered once: February 2018)
One-day course, Participants: 34 people
This course was offered to persons with 6 months to 1 years of experience in GCP QC or monitoring operations. The sessions featured a lecture titled "Practice and Overview of Quality Control" and group discussions of case study exercises focused on quality control operations for "clinical trial documents etc.

GCP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Special Project 3**
Subgroup	**C-T-3**
Theme	**Submission of Public Comments and Well-known of the Contents of Amendments to GCP.**

1) Submission of public comments.
We reviewed the following matters for which public comments had been invited, and submitted our summarized results to the Ministry of Health, Labour and Welfare (MHLW) as official comments of JSQA.

- ICH E17: General Principles for Planning and Design of Multi-Regional Clinical Trials (draft)
- Regulations for Enforcement of Clinical Research Act (draft)
- Guidance for partial revision of "Guidance for 'Ministerial Ordinance on Good Clinical Practice for Drugs'" (draft) (comparison table of old and new versions)
- Basic Rules of the Risk Based Approach to Monitoring Clinical Trials (draft)
  ※We compiled comments on basic concepts relating to clinical trial quality management and reviewed them, but did not submit them as JSQA comments.

For the following matters for which public comments had been invited, we considered the nature and content of the relevant documents but decided not to submit opinions as JSQA and obtained the approval of the Chairperson.

- Ministerial Ordinance for Partial Revision of the Ministerial Ordinance on Good Clinical Practice for Medical Devices (tentative name, draft)
- Ministerial Ordinance for Partial Revision of the Ministerial Ordinance on Good Clinical Practice for Regenerative Medicine Products (tentative name, draft) (draft framework)
- ICH E11(R1): Addendum to the Clinical Investigation of Medicinal Products in the Pediatric Population (draft)
- Draft guideline on good -clinical -practice compliance in relation to trial master file (paper and/or electronic) for content, management, archiving, audit and inspection of clinical trials (EMA)
- ICH E9 (R1): Addendum to Statistical Principles for Clinical Trials: Estimands and Sensitivity Analysis in Clinical Trials (draft)

Revision of opinion consolidation procedure for public comment in JSQA (October 6, 2017)

2) Atypical deliverables
We prepared the following documents to serve as educational materials to make well known of GCP revisions etc. and released them on the JSQA public website.

- Table of comparison of the three GCPs for Drugs, Medical Devices, and Regenerative Medicine Products. (updated version)
- Educational material on "Ministerial Ordinance on Good Clinical Practice for Drugs (January 22, 2016)"
- Educational material on "Implementation of expanded trials of unapproved drugs (Compassionate Use)"
- ICH Reflection on GCP Renovation: Modernization of ICH E8 and Subsequent

Renovation of ICH E6 (We prepared a translation table as a confidential deliverable.)

3) Other
   - Creation of new and old looked off version of Guidance for ‘Ministerial Ordinance on Good Clinical Practice for Drugs(Collaboration with Pocket Materials Preparation Committee: in progress)

GCP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Special Project Group 4**
Subgroup	**C-T-4**
Theme	**Responding to Lecture Requests to the GCP Division, and Managing and Maintaining Lecture Materials**

Special Project Group 4 of the GCP division (C-T-4) began its activities in 2013 based on the theme in the title, and in this 3rd term, we acted with the aim of achieving the following objectives.

1.Purpose of activities

Responding to, and management of "requests for lectures" received by the GCP Division on the basis of the manual.

Planning and performing a JSQA sponsorship seminar for outside.

Storage and management of lecture materials on the basis of the internal manual of "lecture materials" held by the GCP Division.

2. Details of activities

We responded to, and managed the "requests for lectures" on the basis of the internal manual.

We performed the JSQA sponsorship seminar in the 38th Annual scientific Meeting of the Japanese Society of Clinical Pharmacology and Therapeutics.

We stored and managed the "lecture materials" held by the GCP Division on the basis of theinternal manual.

GCP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Special Project 5**
Subgroup	**C-T-5**
Theme	**Globalization of GCP quality assurance activities**

Background of the project:

These days more and more clinical studies are conducted on a global scale. Global clinical studies should be conducted in compliance with ICH-GCP, applicable international regulations, and some specific local regulations that may be applied to some clinical studies.

For this reason, it is of importance for assuring quality of clinical studies that Sponsor, Contract Research Organization, Clinical Investigator, and Site Management Organization keep themselves well informed of these regulations.

Method of the study:

JSQA GCP Division, Special project team 5 studied clinical quality assurance practices that prevail in global settings by the following methods:

- Researched US/EU/British and Asian pharmaceutical regulations, and the regulations related to clinical studies
- Collected the information that is necessary to implement clinical quality assurance activities at the global level
- Held interactive sessions with project team members, and external experts, depending on the topic of study

Given efficiency of research and discussion, Special project team 5 was separated into 3 small groups (Western region: US, EU, and UK), and 2 small groups (Asian region: China, and Korea) in accordance with the country or region studied. However, the former 3 small groups worked together as the group studying the situation in the Western region.

Activities:

1. The group studying the situation in Western region

- Collected and researched the new regulations and guidelines pertinent to pharmaceutical affairs, and clinical studies, which were issued by US Regulatory Authority (FDA), EU Regulatory Authority (EMA), and UK Regulatory Authority (MHRA) during the 13th JSQA term. Then, the list of important new regulations with summary of regulation contents was generated by the group and uploaded on the JSQA webpage for members.
- Collected and researched FDA warning letters for Clinical Investigators, Sponsor (CRO), and IRB in the area of medical drug/medical device GCP inspection, which were issued during the 13th JSQA term. Then, the group generated a database of FDA warning letters and uploaded it on the JSQA webpage for members.
- Held the following 2 seminars whose topics are related to Western countries' regulations in regard to clinical study; the group camp (Aug-2017), and the seminar with British external expert (Sep-2017)

2. The group studying the situation in China

- Collected and researched the new regulations and guidelines pertinent to pharmaceutical affairs, and clinical study, which were issued by the China Regulatory Authority (CFDA). For example, the China study group analyzed the following 2 new regulations which came out during the 13th JSQA term; "The Notice of the Chinese Food and Drug Administration on the inspection of the clinical trial data (2015 117th)", and "the revised China Good

Clinical Practices for Pharmaceuticals (2016)"

3. The group studying the situation in Korea
- Researched "2017 clinical trial inspection basic plan" issued by the Korea Regulatory Authority (MFDS) in 2017
- Analyzed "MFDS Questions & Answers" that are worth noticing among "Questions & Answers related to MFDS regulatory activities" disclosed on MFDS webpage
- Implemented gap analysis between Korea GCP and ICH-GCP
- Implemented survey of "GCP audit conducted toward clinical studies in Korea" for JSQA members

Other: Asian group collaboration working activities
- CFDA/MFDS GCP inspection findings - 37th JSQA Special Project 1 Annual Meeting, Conference for GCP Inspection Case Study, "What's Quality and Compliance?" (Mar- 2017)
- Comparison of Japan/Korea/China GCP inspection - 5th Global QA conference (Nov-2017)

GCP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Special Project Group 6**
Subgroup	**C-T-6**
Theme	**Q&A for GCP Quality Management and Quality Assurance Managers**

It appears that reading through the GCP ministerial ordinance, guidance and notifications does not necessarily yield clear information on how to deal with specific situations encountered in clinical trials. We felt that investigating specific cases might also be an aid to understanding the GCP ministerial ordinance, guidances and notifications.

In the previous (11^{th}-12^{th}) term, Special Project Group 9 and Subgroup C-2-C of the GCP Division looked into commonly encountered cases of audit findings and produced the deliverable, "Q&A for Audit Findings (Examples)," as material to be used by the GCP Division. Special Project Group 6 continued the activities of the previous term, collecting and reviewing issues from commonly encountered cases while avoiding redundancy with other Q&As, and formulating answers. As in the previous term, the deliverable will be summarized into Q&A form and uploaded to the JSQA member website as "Q&A for GCP Quality Management and Quality Assurance Managers," together with the cases prepared in the previous term by Special Project Group 9 and Subgroup C-2-C. For better convenience when searching for relevant cases, the Q&A compilation features a listing categorized by GCP provisions, plus an added search function.