Activity Summary of the 11th Term (April 2012 – March 2014)	
Working Group	Subgroup A, Study Group 1
Theme	Understanding and Introduction of the Quality Management System (QMS)

(Summary)

During the 11th term, Subgroup A, Study Group 1, GCP Division was set based on the following ideas with the theme of, "Understanding and Introduction of the Quality Management System (QMS)."

- To propose the structure of quality assurance in GCP is the task of the GCP Division of JSQA, and also meets the basic idea of QMS. The theme of QMS provides us with an opportunity to directly reconsider the role of staff engaged in quality assurance.
- QMS-related activities have been carried out on a per-project basis in the previous term, but were expanded to activities on a per-study group basis, incorporate the opinions of as many members of staff as possible and to simplify QMS during the 11th term.
- Our aim is to simply show how to view QMS so that our activities can be of some help to propose a structure of quality assurance according to the current situation depending on the level of each company, in reference to the concept of QMS.

After setting up the group, we organized three teams and the three tasks of "Understanding of QMS," "Situation of Each Company in the Industry," and "Introduction of QMS," were set as subthemes for these teams, according to the reasons why individual members participated. Teams cooperated on their tasks in reference to the Japanese-English translation of ISO 9000 family of standards for QMS (JIS Q 9000:2006, JIS Q 9001:2008, and JIS Q 9004:2010) and created the guide, "Understanding and Using the Quality Management System – What is QMS? What is the Current Situation of Each Company? What Are the Advantages of Using it?" (It consists of three parts, presenting the outcomes of each team; refer to the following for the title and a summary of the activities).

Team 1 "Basis of QMS and How to view QMS in GCP"

Once the basis of QMS was understood, Team 1 attempted to interpret QMS in GCP and discussed the differences between ISO and GCP.

Team 2 "Situation of Each Company – Results of Within-Study Group Questionnaire Survey on QMS –"

Team 2 conducted a questionnaire survey on the status of the introduction of QMS techniques in each company, and then tabulated, analyzed, and discussed the survey results.

Team 3 “Introduction of QMS in the Clinical Development Department (GCP)”
Team 3 worked on the relationship between QMS and GCP and the introduction of QMS in GCP-related operations.

Activity Summary of the 11th Term (May 2012 – March 2014)	
Working Group	Subgroup B, Study Group 1
Theme	Introduction of a Risk-Based Approach to Clinical Development Operations

(Summary)
Companies marketing drugs and medical devices spend enormous amounts of time and costs on the compliance of clinical studies with laws and regulations, whereas critical findings are sometimes pointed in the approval review and compliance inspection conducted by the regulatory authorities. On the other hand, it is required to greatly reduce the time spent on the conduct of clinical studies as well as the approval review and compliance inspection by the regulatory authorities.

During the process of the conduct of a clinical study, a scientific approach based on foreseeable risks (risk-based approach [hereinafter, "RBA"]) is considered important as one of the solutions to reduce time and costs. Recently, the FDA and EMA released guidelines on defining the basic idea of the introduction of the concept of RBA into monitoring implemented by the sponsor during the management of clinical studies.

In Japan, "Basic Idea of Risk-Based Approach to Monitoring" was released as an office communication by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare on July 1, 2013, and it is expected to provide a guideline on how to view and use RBA to achieve efficient monitoring. Thus, to efficiently conduct Japanese clinical studies, enhance their competitiveness, and reduce their cost in the future, the introduction of RBA is considered an urgent task.

Subgroup B, Study Group 1, GCP Division worked on concrete methods to incorporate RBA into clinical studies, and to view RBA in contract-based QC/monitoring operations and clinical development and examples of the methodology to use RBA to efficiently conduct clinical studies.

The RBA group on contract-based clinical development operations collected case examples related to business risks in the operations undertaken by contract research organizations, and examined and proposed views about risk assessment (extraction of risks and assessment of the frequency of their occurrence and the degree of their importance) and risk control (avoidance, acceptance, minimization, etc. of risks) and examples of methodology for RBA-based risk management.

The RBA group on QC/monitoring operations reviewed the method and process of using RBA for more efficient operations by focusing their attention on potential causes (hazards) of the occurrence of case examples in accordance with the “Guidelines for Quality Risk Management (dated September 1, 2006). By organizing the categories of “List of Risks,” which were created for submission by Subgroup B, Study Group 1, GCP Division, in the 10th term (Year 2010 – Year 2011), and further focusing their attention on different actions taken in response to the same risk depending on the situation, the group examined and proposed tools to introduce RBA from the individual perspectives of QC and QA.

We expect that the view of RBA and the presented methodology and tools created in the course of our studies will be useful for each company to review its own risk management system.

Activity Summary of the 11th Term (April 2012 – March 2014)	
Working Group	Subgroup C, Study Group 1
Theme	Introduction of CAPA in the GCP Area

(Summary)
In recent years, some companies in every sector of Japanese industry have acquired ISO9000 Series certification, and are making achievements in terms of the construction of an in-house management system, improvement of the quality of products and services, and improvement of employees' awareness of quality, etc. In the pharmaceutical industry, companies began introducing the concept of QMS, and are trying to adopt Corrective and Preventive Actions (CAPA) in the GCP area as a quality control approach.
CAPA is described in the FDA Guidance for Industry Quality Systems Approach to Pharmaceutical cGMP Regulations as well as ICH Q10 Pharmaceutical Quality System (Evaluation and Licensing Division Notification No. 0219-1/Compliance and Narcotics Division Notification No. 0219-1, Pharmaceutical and Food Safety Bureau, MHLW, dated February 19, 2010), and CAPA is therefore penetrating the GMP area in Japanese pharmaceutical companies.
In the GCP area, foreign-based pharmaceutical companies are also introducing CAPA as part of QMS in clinical studies, and the time therefore seems ripe for Japanese pharmaceutical companies to also consider the introduction of CAPA.
As Study Group 1, GCP Division, we set the Year 2012 – Year 2013 theme of "How a CAPA-centered Quality Assurance Unit Should Be," to propose the need to introduce CAPA to the quality assurance system of clinical studies.
We as Subgroup C worked on the introduction of CAPA in the GCP area from the viewpoints of the extraction of issues arising from the introduction of CAPA to the quality assurance system, the clarification of the process of improving the issues, conversion to preventive action-centered quality assurance activities, and reflection from the viewpoint of the GMP area. We have consequently summarized the necessary information to introduce CAPA to the GCP area as well as the tools and analyses to efficiently operate CAPA, incorporated knowledge necessary to introduce CAPA, and created a document as an introductory guide for the staff of pharmaceutical drug-related companies that consider the introduction of CAPA.

Activity Summary of the 11th Term (April 2012 – March 2014)	
Working Group	Subgroup A, Study Group 2
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 1 −

(Summary)

We worked on the introduction of the concept of Q8 and Q9, which are ICH Quality Guidelines for pharmaceutical development, into GCP audits to propose harmonization of the basic idea with the actual methods beyond the boundaries of regions and audit facilities aiming at effective and efficient implementation of GCP audits in global clinical trials. We first selected the "process of revision of the written informed consent form with regard to serious adverse events (SAEs)" among the set of processes involved in the preparation of completed case report forms, which are the "final products" of the clinical trial. We then identified critical process parameters (CPP) that have to be controlled during the preparation of the revised written informed consent form, which is an intermediate product of the concerned process, and then examined whether the relevant CPP-centered auditing is possible or not based on the results of "fact-based analysis" of case examples. The analysis was performed using the database, "Complete Case Examples of GCP Inspection Reports obtained by using the Official Information Disclosure System" which was compiled by Special Project Group 1 of the GCP division over six years from 2006 to 2012. We divided the concerned process into 9 sub-processes, and analyzed cases (harm) that arose in each sub-process, CPPs related to the concerned harm, and details of the deviations of CPPs (hazards). As a result, it was revealed that the occurrence of harm in the concerned process was localized to specific sub-processes and the localization profile remained unchanged over time. We then analyzed these harm-related CPPs and the details of the deviations, and found the location and contents of the deviation in the concerned CPP. These facts suggest that it will be possible to effectively and efficiently implement audits beyond the boundaries of regions and audit facilities by implementing these CPP-centered audits at least during the "process of revision of the written informed consent form in terms of SAEs" among the production processes in Japanese clinical trials.

Further analyses are necessary to clarify whether it is possible or not to introduce these concepts into other processes than the analyzed process among the production processes in Japanese clinical trials, in other words, whether it is possible or not to define the existence of "generality" among the processes, and also whether there are "regional differences" in the "CPP that should be controlled" by comparing, analyzing, and evaluating the results of GCP inspections in Japan, the US and Europe, to not only harmonize the basic concept of auditing as well as its practical implementation methods beyond the boundaries of regions and audit facilities, but also investigate actual measures for "Built-in Quality" in each production process in clinical trials.

Activity Summary of the 11th Term (April 2012 – March 2014)	
Working Group	Subgroup B, Study Group 2
Theme	Improvement in Practical Interview Techniques and Use in Audit Activities − Final Chapter −

(Summary)
During this term, Subgroup B, Study Group 2 worked on the following tasks over two years with the aims of improving the practical interview skills of auditors, apply interview techniques to audit activities, and return educational materials to member companies, taking over the task of Subgroup C, Study Group 2 in the previous term, which was “Improvement of Interview Techniques and Interview-focused Audit Techniques.”

1) Implementation of practical roll-playing in various audits to improve interview skills
2) Creation of educational materials for auditors

Among 22 Subgroup B members of Study Group 2 in this term, only 5 members of staff from Subgroup C, Study Group 2 continuously participated in the previous term. Thus, we first started to understand the basis of interviewing by reading the submitted document (11C15) of the previous term, and then worked on the tasks by using each meeting as an opportunity to improve practical interview skills.
With regard to the task of the implementation of practical roll-playing listed in the above 1), we closely examined checkpoints in case no problems were found with the audit on an investigator's site (Pharmacy, Laboratory, and Clinical Study Administrative Office, etc.) and the in-house system (Phamacovigilance activities), as well as general checkpoints in the audit of vendors (Monitoring activities, Data Management activities, and Statistical Analysis activities), and implemented roll-playing for interviews. With regard to the task of auditing at investigators’ sites, we tried to improve interview skills of group members by assuming six problem cases and carrying out practical mock interviews.
With regard to the task of working on educational materials for the staff in charge of auditing listed in the above 2), we compiled our 2-year work outcomes as a third section in this document, and also held a new training course titled, “Interview Skill Upgrading Course for Auditors” on November 29, 2013, jointly with Special Project Group 3.
We are also currently preparing e-learning materials to improve audit-related interview skills as educational materials for member companies, and plan to release it on JSQA’s website in fiscal year 2014.
We hope that these e-learning materials will contribute to construct a system for

educational skill upgrade training in a variety of aspects in the future JSQA, and expect that the work outcomes of Subgroup B, Study Group 2 during this term will be helpful during practical audit activities, and will improve the interview skills of auditors.

Activity Summary of the 11th Term (April 2012 – March 2014)	
Working Group	Subgroup C, Study Group 2
Theme	Toward the Construction of a Guideline for Quality Assurance for Clinical Studies − Proposal of a Clinical Trial Quality Assurance (CTQA) Model −

(Summary)
Subgroup C, Study Group 2 (hereinafter, this group) worked on the task of "Construction of a Quality Assurance System for Clinical Studies."
We were engaged in our task to discuss what system is needed, what operations are essential, etc., to complete the quality assurance system in clinical studies, which were mentioned as the next-term task in the report of Special Mission Project D during the previous term titled, "Relationship between Quality Control, Auditing, and Quality Assurance in Clinical Studies –JSQA's Views − (11C07), and formulate a guideline for a quality assurance system in clinical studies.
The final goal that was originally assigned to this group during this term was to remove the boundaries between the audit department, the QC department, and the monitoring department, etc., and to create a guideline to complete the quality assurance system. During the working process, we focused our attention on similarities between the quality assurance of clinical studies and the quality assurance of software development in the IT industry, and proposed as our task for this term, the "Clinical Trial Quality Assurance (CTQA) Model" that was created by applying the V Model used during software quality assurance of clinical studies.
We decided to use the term, "quality assurance (shitsu-hosho)" model, instead of the term, "quality assurance (hinshitsu-hosho)" model. The term "shitsu-hosho" is often used to assure "shitsu (quality)" of processes, since we use the phrase shitsu-hosho of medical services (quality assurance of medical services), and we therefore consider that it is more appropriate to use the term "shitsu" because a clinical study itself is not a deliverable, but we assure its process. The term "hinshitsu-hosho (quality assurance)" is also prone to give the image of conventional quality assurance activities that are centered on checking up, and consist only of audit-based activities. We therefore chose this term, implying that we hope to dispel this old-fashioned image from future quality assurance operations.
Since "Quality Assurance" is defined in the ISO9000 Series, some people may feel that something is wrong; however, it is mentioned in the definition of quality (hinshitsu/shitsu) by the Japanese Society for Quality Control that the term "shitsu" is used for processes. We therefore decided that there would be no problem using the term

"shitsu-hosho" in this report.
We hope that the CTQA model we proposed in this report can be used as a tool for each company to construct a quality assurance system for clinical studies.

Activity Summary of the 11th Term (April 2012 – March 2014)	
Working Group	Subgroup A, Study Group 3
Theme	Examination of What Quality Assurance Should Be for Data, Documents, and Records using the Computerized System from Global Perspectives

(Summary)
Subgroup C3A worked on a proposal about ePRO and a checklist (draft) for compliance investigation, taking over the theme of the previous term, “Examination of What Quality Assurance Should Be for Data, Documents, and Records using the Computerized System from Global Perspectives.” The ePRO is a tool to capture data that were conventionally collected on a paper basis as electromagnetic (electronic) data, as with EDC.
To date, Subgroup C3A (C4A in the 9th term and C3A in the 10th and 11th terms) has worked on the examination of EDC on the client side, the examination of EDC on the CRO/SMO side, and making propositions about the EDC check sheet (draft), and has provided opportunities to discuss EDC and contributed proposals during the initial stages of EDC. During this term, based on the assumption that ePRO is facing similar problems as those encountered during the initial stage of EDC, we were engaged in a field survey and the examination of issues arising during the introduction of ePRO, and also worked on the proposal about the latest version of the checklist that was the outcome of the “Examination of the Proposal About a Checklist for Compliance Investigation,” which was favorably accepted during the previous term.

Activity Summary of the 11th Term (May 2012 – March 2014)	
Working Group	Subgroup B, Study Group 3
Theme	Examination of Quality Assurance Activities for GCP-related Electromagnetic Records

(Summary)

In view of the recent worldwide trend of institutionalization of regulatory requirements for use of electronic records/electronic signatures (hereinafter, ER/ES) in response to advances in systematization of information, requirements under the laws and regulations as well as industry standards have recently been examined in Japan.

Based on the latest regulatory requirements regarding documents pertinent to application for manufacturing and marketing approval of pharmaceutical drugs etc., clinical study-related records (documents and data) that should be archived at the sponsor's side, and paper-based source documents including CRFs, it became legally possible to create, archive, and deliver the documents in electronic form and regard the electronic data as the original data.

With rapid advances in computerization of documents in environments surrounding clinical studies, individual pharmaceutical companies take measures (verification etc.) to respond to this situation. On the other hand, we do not see much progress with the arrangements to formulate a guideline etc. for verification methods of the information system etc. in Japan, and it is anticipated to standardize a set of operations including quality assurance activities in response to computerization.

Before starting to work on our tasks for this term, we discussed the following three themes, including the ongoing theme from the previous term (FY 2010 – FY 2011; hereinafter "10th term").

1) Explanations about the items in CSV documents that are developed during CSV activities, to be reviewed by QA person(s) and the review points

We integrated the contents of the reports from the past two terms (the FY 2008-FY 2009 term and the 10th term), when the perspective of quality assurance on computerized system validation (CSV) documents were examined and reviewed.

2) ER/ES- and CSV-related materials for "educators"

Based on the results of the "Questionnaire Survey on Quality Assurance Activities in the GCP Area" conducted in the 10th term, we considered it meaningful to provide materials for educators, and created materials for educators titled, "GCP, CSV, and QMS."

3) Comprehension and understanding of the trend of ER/ES regulatory requirements

We revised the "Revisions history of MHLW Ordinance No. 44," and the "Quick Reference Matrix for MHLW Ordinance No. 44 and GCP Ordinance, and Notifications

for their Operation," which were created in the 10th term.

Activity Summary of the 11th Term (April 2012 – March 2014)	
Working Group	Subgroup C, Study Group 3
Theme	Preparation of CSV for Statistical Analyses − Based on the Guideline on Management of Computerized Systems for Marketing Authorization Holders and Manufacturers of Drugs and Quasi-drugs −

(Summary)

Many pharmaceutical companies and CROs use double programming for quality control of statistical analyses in clinical studies. Double programing assures the interpretation of specifications and the accuracy of programming by ensuring that the results of programs by independent programmers are consistent.

On the other hand, Computerized System Validation (CSV) is often used in computer-based systems, and CSV is required in case Electronic Data Capture (EDC) is used. The Guideline on Management of Computerized Systems for Marketing Authorization Holders and Manufacturers of Drugs and Quasi-drugs was also released in 2010, and it is becoming highly likely that a response to CSV is required in future statistical analysis operations in clinical studies.

We, group C3C, tried the potential implementation of CSV in accordance with this guideline. However, since this guideline is based on GMP and GQP, we faced several problems, e.g., there were many descriptions related to hardware such as manufacturing equipment, the the assumed operation period was different from that of the statistical analysis operations involved in clinical studies. We therefore proposed to implement only the necessary elements by interpreting the statistical anlaysis operations in clinical studies based on the concept of this guideline.

Activity Summary of the 11th Term (April 2012 – March 2014)	
Working Group	Subgroup A, Study Group 4
Theme	Disseminating the concept of source document management − Training materials for learning the ALCOA principal –

(Summary)
With regard to the quality required for source documents, ALCOA-CCEA, which consists of ALCOA (Attributable-Legible-Contemporaneous-Original-Accurate) issued by FDA and another four elements (CCEA: Complete-Consistent-Enduring-Available when needed) added by EMA, has been proposed. With the increase in the number of global studies, various efforts have been made to promote the spread of ALCOA(-CCEA) principles in Japan. As a result, the importance of source document management based on ALCOA is becoming prevalent in individuals involved in clinical studies.
However, since the interpretation of ALCOA differs among sponsors, as well as between the sponsor and the medical institutions, it seems that source document management does not function properly in the clinical setting.
We therefore decided to create a basic guideline on learning how to maintain reliable source documents, rather than just memorizing the meaning of ALCOA.

As a result of group activities over a period of 2 years, we created training materials for new monitors/CRCs, or monitors/CRCs who know the meaning of ALCOA, but not how to implement it at clinical sites. Each case study in the training material consists of “aim,” “background,” “question,” “answer,” and “explanation.” The training material is designed to show what should be learned by describing the “aim” at the beginning of each case study. We hope that this training material can be used to introduce training and continuous training in individual companies (sponsor, CRO and SMO) and medical institutions.

Activity Summary of the 11th Term (April 2012 – March 2014)	
Working Group	Subgroup B, Study Group 4
Theme	QA/QC in Investigator-initiated Clinical Studies and Clinical Research

(Summary)
Our group has worked on our task of "QA/QC in Investigator-initiated Clinical Studies and Clinical Research" for two years. It is not an exaggeration to say that the quality of clinical research data have attracted social attention in these two years. Particularly sensational incidents include false coverage of the world's first clinical application of iPS cells, suspicion about the artificial manipulation of clinical research data concerning "valsartan," a drug for the treatment of hypertension, and retraction of a published paper used for promotional activities. On the other hand, the Japanese government began reviewing the "Ethical Guidelines for Clinical Research" in December 2012; however, during the review process, improvement of the quality of clinical research was also found to be an important subject, and review is underway.
Under these circumstances, our group worked on "Comparison and Assessment of the Differences in Regulations in Company-sponsored/Investigator-initiated Clinical Studies/Research," "Monitoring and Auditing Case Examples based on Experience in Investigator-initiated Clinical Studies/Research," and "Questions on Investigator-initiated Clinical Studies/Research."
Based on these working results, we compiled public comments to be officially submitted by JSQA in response to "Recruitment of Opinions on the Interim Report on the Review of the Ethical Guideline for Epidemiological Research and the Ethical Guideline for Clinical Research," which was officially announced on September 24, 2013. We also created a draft proposal about quality assurance in clinical research addressed to the Director of the Evaluation and Licensing Division as well as the Assistant Vice-Minister of MHLW. We believe that our group accomplished a great achievement in terms of compiling public comments and a draft proposal.

Activity Summary of the 11th Term (April 2012 – March 2014)	
Working Group	Subgroup C, Study Group 4
Theme	Points to Consider during the Conduct of a Global Study in Japan

(Summary)
Focusing our attention on points to consider during the conduct of a global study in Japan, our group created a report that could be released and used practically at study sites, by listing global study-specific procedures, under the circumstances where China, Taiwan, Korea, etc., have been surging ahead of Japan in the conduct of global studies initiated by Western countries.
At first, we collected 159 case examples of specific problems arising during the conduct of a global study from among Subgroup C members. Next, to conduct a questionnaire survey of clinical research collaborators working at the frontline of clinical studies, we closely examined each of the 159 case examples from the standpoint of whether they were appropriate for use in a questionnaire survey or not, and created a questionnaire comprised of 17 items and approximately 70 questions. We requested a member company of the Japan Association of Site Management Organizations to conduct a questionnaire survey during the period from May 13 to July 19, 2013, and received answers from 245 clinical research collaborators at 23 companies over about two months. Some of the survey results were presented at a poster session of the “13rd Conference to Review What CRC and Clinical Studies Should Be, in 2013 in Maihama.”
We compiled the results of the questionnaire survey, and briefly summarised the results, discussion, and a proposal on the issues that should be noted among the items in the questionnaire as points to consider during the conduct of a global study.
This report can hardly be considered adequate, because we created questionnaire items based on problem case examples extracted from limited members within a limited time frame. Nevertheless, we expect that this report will contribute to the improvement and efficiency of quality control/assurance and that it can be helpful during the conduct of a global study in Japan.

Activity Summary of the 11th Term (May 2012 – March 2014)	
Special Project Group	Special Project Group 1
Theme	Examination of Case Examples of Compliance Review/Inspection

(Summary)

Special Project Group 1 collected, examined, and analyzed compliance reviews by PMDA [Japan and overseas] (128 reports), which were reported by members of the GCP Division of JSQA, case examples of inspections by overseas regulatory authorities (3 reports), and case examples of compliance reviews obtained from PMDA by using the Information Disclosure Law (150 reports). To investigate the status of each company to address the items instructed by compliance review, we conducted a within-group questionnaire survey. With regard to inspections by overseas regulatory authorities, we collected information including related regulations mainly from published information.

We presented these working results at the "What's a Quality & Compliance? – Review Meeting on Case Examples of Compliance Reviews/Inspections –," which is held annually, and gave feedback to the JSQA members.

1) Conferences

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

- 33rd: March 22, 2013, Nissho Hall, Tokyo (approximately 650 participants attended)
  – Case examples of compliance reviews by PMDA and within-group questionnaire results
  – Trend of inspections by overseas regulatory authorities
  – PMDA's special lecture: EDC System Sheet
- 34rd: February 19, 2014, Nissho Hall, Tokyo (approximately 650 participants attended)
  – Case examples of compliance reviews by PMDA and within-group questionnaire results
  – Trend of inspections by overseas regulatory authorities
  – Invitation lecture: Experience with EMA Inspections

(2) Website-based basic course

To enhance understanding at the Review Meeting on Case Examples of Compliance Reviews/Inspections, we developed a course in basic knowledge and information with compliance review of individuals with little experience in compliance review, and

released the contents on the JSQA website throughout the year.

2) Concrete results

- Database of case examples of compliance reviews collected using the Information Disclosure Law [released on the JSQA website]
- Summary of review results (33rd and 34th meetings) [distributed to participants in review meetings and to companies that provided case examples]
- GCP compliance review reporting materials (33rd and 34th meetings) [distributed to participants in review meetings and to companies that provided case examples]

3) We additionally worked on the following activities

- January 2013: Presentation of PMDA's compliance review at Taiwan SQA
- September 2013: Session planning at the “13th Conference to Review How CRC and Clinical Studies Should Be, 2013 in Maihama” (chairman, presentation, and panelists).
- December 2013: Presentation about PMDA's compliance review at the RQA South East Asia Regional Forum

Activity Summary of the 11th Term (April 2012 – March 2014)	
Special Project Group	Special Project Group 2
Theme	Collection/Analysis/Use of Information on Overseas Inspections by FDA.

(Summary)

CT2 worked on four topics during this term. A description of our activities and the resulting materials we produced are as follows.

1. Aggregation of Information on the Latest FDA Warning Letters from CDER (Center for Drug Evaluation and Research) or CBER (Center for Biological Evaluation and Research))

From the warning letters that CDER and CBER released on their websites, we extracted a total of 23 reports issued to clinical investigators, sponsors, and IRBs during the period from February 16, 2011 to June 1, 2012, and constructed a spreadsheet.(There were no reports addressed to sponsors).

The spreadsheet contains information on each warning letter, including the URL (with a hyperlink function), address, country, date of insurance, as well as a summary (including examples), the clauses of the Code of Federal Regulations Title 21 (CFR Title 21) that were violated, possibly corresponding ICH GCP items, etc.

This spreadsheet allows easy search of a number of examples for each CFR Title 21 clause and ICH GCP item, and is deemed useful to understand recent FDA regulations, noncompliance case examples, and characteristics of GCP inspections by FDA.

2. Comparison and Assessment of a Simple Translation of the Compliance Program Guidance Manual, a Manual for FDA's GCP Inspections, and the Checklist for PMDA's Reliability Investigation

Based on the "Compliance Program Guidance Manual; Chapter 48 - Bioresearch Monitoring (CPGM)" a manual for FDA's GCP inspections, we examined the following CPGMs.

– CPGM 7348.810 – SPONSORS, CONTRACT RESEARCH ORGANIZATIONS AND MONITORS (MAR/11/2011)

– CPGM 7348.811 - CLINICAL INVESTIGATORS AND SPONSORS – INVESTIGATORS (DEC/8/2008)

In a comparison table, we provide a brief translation of "PART III - INSPECTIONAL," which contains descriptions of the inspection procedures, viewpoints, and other descriptions, as well as "PART V - REGULATORY / ADMINISTRATIVE STRATEGY," which contains descriptions of the inspection results, their handling, case examples and conclusions about the "Official Action Indicated," etc., compared it with

the checklist of PMDA's reliability investigation, and examined the differences between the US and Japanese inspections, and described the items considered to be specific to each of Japan and the US.
The resulting document provides information that is considered useful for the sponsor to appropriately conduct a clinical study and appropriately respond to an FDA inspection.

3. Building Quality into Clinical Trials – Risk-based Clinical Study Design, Conduct, Management, and Quality Assurance −

FDA released a draft guidance on risk-based monitoring in August 2011 and EMA released a draft reflection paper on risk-based quality management in clinical studies; two years later FDA and EMA released their official versions in August and November 2013, respectively. These guidelines etc. propose that the most important tool to ensure subject protection and data reliability in clinical studies is a well-designed and clearly described protocol. What is necessary to achieve this purpose is to create a protocol in which important risks related to subject safety and data reliability are identified in advance, and then eliminate or minimize them. Items to be monitored are well defined, and by implementing monitoring in accordance with a monitoring plan that reflects the risk management plan, risk management is performed on an ongoing basis and assures the required quality.
Based on the information released on the websites of related organizations including FDA, EMA, and Clinical Trial Trans Formation Initiative (CTTI), Section 1 to Section 7 of the resulting document provides overviews of the definition of quality in clinical studies, "Building Quality into Clinical Trials," which incorporates the concept of Quality by Design / Quality Risk Management into clinical studies - elements that should be contained in the protocol to conduct a high-quality clinical study and risk-based monitoring.
Section 8 describes the concept of "Risk-based Clinical Operation Cycle," which was constructed by combining individual functions necessary to achieve risk-based monitoring, in view of the elements described in Section 1 to Section 7. This cycle creates a mechanism by which the decision-making body serves as a playmaker in quality control and coordinates the advantages of central and on-site monitoring, thus allowing more reasonable monitoring of the quality of the clinical study in accordance to the monitoring plan compared with conventional monitoring based entirely on on-site monitoring. This cycle is also intended to update the monitoring plan on an ongoing basis, rationalize risk detection, assessment, and minimization measures, and eventually implement Corrective Action & Preventive Actions (CAPA), thereby keeping risks within the quality range planned in advance.

Section 9 also describes an approach to auditing. We believe that risk-based auditing becomes possible by assessing risks in this risk-based clinical operation cycle and conducting audits according to the risk assessment, thereby improving the function of this cycle, as well as checking via an audit through which monitoring is implemented based on this cycle according to the monitoring plan that is updated on an ongoing basis.
In various parts of the text as well as in Section 11, "Appendix," information that is considered useful is released by individual organizations, including their URL (with a hyperlink function), and typical illustrations are introduced.

4. Introduction of GCP Regulatory Information etc.
We translated the following guidelines etc., and released them in August 2012 on the JSQA website.
– "Guidance for Industry: Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring (DRAFT, Aug/2011, FDA)"
– "Reflection paper on risk-based quality management of clinical trials (Draft, Aug/2011, EMA)"
FDA and EMA released their official versions in August and November 2013, respectively.

Activity Summary of the 11th Term (May 2012 – March 2014)	
Special Project Group	Special Project Group 3
Theme	Holding of Training Courses for Staff in Charge of Auditing/Quality Control

(Summary)

In addition to 5 types of training courses that have conventionally been held for staff in charge of auditing/quality control, we newly held a course related to interview skills, jointly with Subgroup B, Study Group 2, a total of 10 times over 2 years in a single term.

Members who participated in Special Project Group 3 could enhance their knowledge and understanding of quality control, auditing, and quality assurance in the GCP area through the discussions on holding the course.

[Courses Held and an Outline of them]

QC/QA Beginner's Course (held twice, namely, in November 2012 and July 2013)

To learn basic knowledge about QC/QA in the GCP area, this course consisted of "Overview of QC/QA," "Overview of the Pharmaceutical Affairs Law and GCP," and "Q&A Session," and was held using a classroom teaching style (1 day).

The number of participants was approximately 100 per session.

Basic Course for Staff in Charge of Clinical Quality Control (held twice, namely, in November 2012 and October 2013)

Focusing on quality control operations for "clinical study-related documents etc." for staff with 1 to 3 years' experience of quality control operations or monitoring operations in the GCP area, this course was held using a classroom teaching style including a group discussion (1 day).

The number of participants was approximately 50 per session.

Advanced Course for Staff in Charge of Clinical Quality Control (held once in December 2013)

For staff in charge of practical QC operations and monitoring operations in the GCP area (those capable of discussions based on the standards for QC operations of their own companies [essential documents]), this course was held using a style that focused on an active discussion with people working in other companies in the same industry based on the experiences of individual participants (1 day).

The number of participants was 42.

Basic Course for Staff in Charge of Clinical Auditing (held twice, namely, in November 2012 and July 2013)

This course consisted of "Overview of GCP Auditing," "Introduction of Audit Methods of Each Company (presentation of audit methods of two companies)," and "Panel Discussion," and was held using a classroom teaching style for staff who have less than approximately 3 years' experience of GCP audit operations (1 day).

The number of participants was approximately 60 per session.

Advanced Course for Staff in Charge of Clinical Auditing (held twice, namely, in February 2013 and February 2014)

Providing a mock audit on a medical institution, this course was held using a group work style to improve audit skills necessary for auditing medical institutions, including the thinking process, information collection by document review, information collection by interviews, and feedback to the auditees of information collected (two days). With the cooperation of Hamamatsu University School of Medicine, the principal investigator, CRC, and administration office staff who are actually involved in clinical study operation cooperated with the interview session, and it helped us to have practical trainings.

The number of participants was approximately 35 per session.

Upgrading of Interview Skills Course for Staff in Charge of Clinical Auditing (held once in November 2013)

This course was started for the first time during this term and was held using a group work style to improve interviewing skills, important skills for information collection during audit operations (1 day). We held this course jointly with Subgroup B, Study Group 2, which was working on "Improvement of Practical Interview Techniques and Use in Audit Operations" as the group theme. We gained the cooperation of the members of Subgroup B, Study Group 2, and used the materials they produced during the previous term, and they also served as lecturers on the day of the lecture and tutors for each group, etc.

The number of participants was 36.

Activity Summary of the 11th Term (April 2012 – March 2014)	
Special Project Group	Special Project Group 4
Theme	Creation of the Guideline for Global Auditing Appendix (Trilateral Agreement)

(Summary)

Under the Special Project of the GCP Division of JSQA, we submitted a manuscript titled, "The Guideline for GCP Auditing" to Clinical Evaluation in 2007, and a manuscript titled, "The JSQA Guideline for GCP Auditing" to QA Journal. Subsequently, an agreement to create a common guideline was reached among the three organizations, the Society of Quality Assurance (SQA), the British Association of Research Quality Assurance (BARQA), and JSQA, and JSQA, SQA, and Research Quality Assurance (RQA; BARQA at the time) agreed upon the "Global Guideline for GCP Audit" in 2009. During the process of working on this guideline, we agreed to keep core elements in the main body of the guideline and supplemental elements in appendices. Special Project Group 4, GCP Division is now taking over this activity. During this term, we worked on this task with the aim of reaching an agreement on all appendices and to present the outcomes of our activities through a panel discussion with SQA and RQA at the 4th Global QA Conference scheduled in Las Vegas in April 2014. During the working process, we closely communicated with each another, holding four face-to-face meetings (8th to 11th) and three telephone meetings with SQA and RQA. We will present the outcomes of our work at the 4th Global QA Conference and also plan to release them as a Japanese version to JSQA members by the end of the first half of 2014.

◆ Face-to-Face meeting

8th Face-to-Face meeting (SQA Annual meeting in Miami)
9th Face-to-Face meeting (BARQA Annual conference in Manchester)
10th Face-to-Face meeting (SQA Annual meeting in Indianapolis)
11th Face-to-Face meeting (1st European Quality Assurance Conference in Bonn)

◆ Appendix

- Risk-based Approach
- CAPA
- Grading Audit Findings
- DM/EDC vendor audit
- IRT vendor audit
- Investigator site audit

- EMR audit
- CRO audit
- Clinical laboratory audit

Activity Summary of the 11th Term (April 2012 – March 2014)	
Special Project Group	Special Project Group 5
Theme	Submission of Public Comments and Notification of the Contents of Amendments to GCP etc.

(Summary)

1) Submission of public comments

In response to the recruitment of "Opinions on the Ordinance for the Partial Revision of the Regulations for Enforcement of the Pharmaceutical Affairs Law (draft)," Special Project Group 5 recruited opinions from its members, reviewed them, and compiled them as opinions that should be submitted from the position of JSQA. This was reviewed and approved by the Secretariat of the GCP Division, and submitted to the Minister of Health, Labour and Welfare in the name of the "Secretariat of the GCP Division of JSQA."

Opinions summarized on the following points by other groups were submitted to the Minister of Health, Labour and Welfare through our project group.

- Recruitment of Opinions on the "Ordinance on the Partial Revision of the Regulations for Enforcement of the Pharmaceutical Affairs Law and Ordinance on Good Clinical Practice for Medical Devices (Draft)"
- Recruitment of Opinions on the "Interim Report on Review of Ethical Guidelines for Epidemiology Research and Clinical Research"

2) Notification of the contents of GCP amendments

As educational materials to provide a clear understanding of the revised points, we created, "Notice about Amendments to the GCP Guidance 'Ordinance for the Partial Revision of the Regulations for Enforcement of the Pharmaceutical Affairs Law'" and released this on the JSQA website.

We also created the following documents jointly with the "Committee for clinical study handbook" and released them on the JSQA website.

These documents were introduced in the "Center News" published by the Center for Clinical Trials, Japan Medical Association.

(1) Revisions of the following guidance issued on December 28, 2012: "Guidance for the Ministerial Ordinance on Good Clinical Practice for Drugs (Director-General Notification No. 1228-7, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated December 28, 2012)"

(2) Revisions of the following guidance issued on February 14, 2013: "Clinical Study-related Documents and Records (Office Memorandum of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated

February 14, 2013”

3) We held a workshop on “Basic Concept of Using Electromagnetic Records in Clinical Study-related Documents” issued as of July 1, 2013, within the group, and made efforts to understand the Office Communication.

Activity Summary of the 11th Term (April 2012 – March 2014)	
Special Project Group	Special Project Group 6
Theme	QC/QA during Clinical Studies of Medical Devices

(Summary)
While it is required to conduct high-quality clinical studies of medical devices, as for drugs, since the Ministerial Ordinance on Good Clinical Practice for Medical Devices was enforced in 2005, the present situation is that there are many cases for which a clinical study is not required under the pharmaceutical regulations on the application for approval, or that even if a clinical study is required, it is sometimes possible to make an application using overseas clinical data.
Therefore, remarkably few clinical studies of medical devices are conducted in Japan, compared with those of drugs. There are also medical device-specific issues, such as a short duration between model changes, and it is often difficult for companies to maintain the clinical study operation system.
Medical devices also cover a wide range, and it is necessary to conduct a clinical study by considering the characteristics of medical devices more intensively than drugs; it is therefore necessary for companies etc. intending to conduct a clinical study of a medical device to obtain experience, but in fact, they do not have the opportunity to conduct clinical studies to gain experience.
In this way, the situation remains that it is harder to accumulate experience with a clinical study of medical devices, compared with that of pharmaceutical drugs, and our group has therefore discussed tasks and issues to conduct a clinical study of a medical device. This time, we found how much these tasks and issues affect the overall clinical study of medical devices (risk: combination of hazard probability and magnitude of the hazard) remained unexamined, and therefore we considered that we should work on this subject.
We then conducted risk assessment, referring to ISO 14971: 2007 (JIS T 14971:2012) in terms of how to recognise these effects in concrete terms, and worked on medical device-specific critical issues. For subsequent tasks, such as how individuals actually involved in clinical studies of medical devices recognise these effects as well as the proposal of concrete procedures and methods (particularly measures for risk minimization etc.), however, we will work on them during the next and subsequent terms.

Activity Summary of the 11th Term (May 2012 – March 2014)	
Special Project Group	Special Project Group 7
Theme	Examination of Asian Clinical Study Environment/Regulatory Requirements

(Summary)
Our group's task is to collect and review specific information on actual GCP inspections by regulatory authorities based on the comparison of clinical study environments in Asian countries. Among participating group members, we did some brainstorming about questions we usually had in mind about the conduct of clinical studies and quality assurance in clinical studies conducted in Asian countries, and found that we wanted to confirm the quality assurance system, actual status of inspections, etc. of regulatory authorities of Asian countries.
Particularly, it was unknown how a clinical study is conducted in accordance with specific provisions of the GCP of each country, which is different from ICH GCP, as well as the regulations applied to the country, in which the clinical study is conducted, and how an inspection is conducted by regulatory authorities after application. We consider that it is most efficient to have hearings about these kinds of information from group members as well as staff who have participated in the GCP Division, and then conducted a hearing-based questionnaire survey during the period from December 2012 to June 2013.
In parallel with these activities, we divided our group into three teams and worked on information collection in the three countries of Korea, Taiwan, and China, which attracted the highest interest among members. Our activities during this term are reported as follows.
Team for Korea: Overview of regulatory authorities, actual status of inspections (revised method of the investigation of medical institutions), checklist for inspections, and K-GCP revision table
Team for Taiwan: Overview of regulatory authorities, actual status of inspections, checklist for inspections
Team for China: Overview of regulatory authorities, actual status of inspections, checklist for inspections
Under this project, we worked on our task, making efforts to present specific case examples by using hearings and we hope that our activities will be helpful during individual audit operations.
We hope that our work outcomes will be helpful during JSQA members' daily audit operations.

Activity Summary of the 11th Term (April 2012 – March 2014)	
Special Project Group	Special Project Group 8
Theme	Collection of Information from Stakeholders in Clinical Development, Analysis of the Information Collected, and Proposals Based on the Analysis Results

(Summary)

To organize and understand issues in clinical development (including global studies) arising on the pharmaceutical company side (including CROs), we collected information from study sites, regulatory authorities, and stakeholders such as parties involved in the industry, analyzed the collected information, and made a proposal based on the analysis.

1. Understanding of ICH-GCP based on the International Standards for Quality Management System (ISO 9001:2008) etc.

[Hypothesis] Is it necessary to correctly understand ISO 9001:2008 (International Standard for Quality Management System) and ISO 19011:2011 (Guidelines for Auditing Management Systems) to understand the nature of ICH-GCP?

[Verification] Among the group members, we made comparisons and verifications of ICH-GCP and the International Standards (ISO 9001:2008 and ISO 19011:2001) with ISO 9001 specialists.

[Conclusion] It is useful to correctly understand the International Standards (ISO 9001:2008 and ISO 19011:2011) to understand the nature of ICH-GCP.

2. Pilot approach to the "Workshop on ISO 9001 and ICH-GCP" for the GCP Division

[Hypothesis] Is the "Workshop on ISO 9001:2008 and ICH-GCP" by ISO 9001 specialists for GCP Division members useful for them to understand the nature of ICH-GCP?

[Verification] A pilot comparison and verification of ICH-GCP and the International Standards (ISO 9001:2008 and ISO 19011:2011) was conducted with ISO 9001 specialists for GCP Division members.

[Conclusion] It is useful to correctly understand the International Standards (ISO 9001:2008 and ISO 19011:2011) for GCP Division members to understand the nature of ICH-GCP.

3. Proposal for the "Workshop on ISO 9001 etc."

In consultation with the related departments (board of education etc.) on the operation of the "Workshop on ICH-GCP and ISO 9001:2008" by ISO 9001 specialists for GCP Division members, we aim to perform regular operations. We also consult with the related departments (board of education etc.) on the possibility of pilot operation of

similar workshops on ISO 9001 for other divisions within JSQA than the GCP Division.

Activity Summary of the 11th Term (May 2012 – March 2014)	
Special Project Group	Special Project Group 9
Theme	Q&A for Audit Findings (Examples)

(Summary)
We collected case examples focusing on familiar audit findings, and discussed them at the group's monthly meetings. Changes that arose during this period included an amendment to the GCP Ordinance, abolition of the Notification of Operation of GCP, and issuance of the GCP Guidance, all of which were announced in December 2012, in order to efficiently conduct clinical studies by conforming the contents of the Japanese GCP Ordinance and Notification of Operation of GCP to the contents of ICH-GCP. In this GCP Guidance, it is stated that, "a clinical study may be conducted by appropriate operating procedures covered by this guidance, as long as compliance with the GCP Ordinance assures the protection of human rights, the maintenance of safety, and improvement of the well-being of trial subjects, as well as the scientific quality of the clinical trial and the reliability of the trial results." This statement suggests that there are acceptable margins for appropriate alternative methods that we can choose as long as the intent of GCP is met. Uniform forms were also reviewed in March 2013, and measures for efficiency, simplicity and other improvements were taken for all uniform forms by abolishing the requirement for preparing the original and copies of it, and asking only the minimum level of information required under the ordinance.
Referring to examples from publicly available GCP-related practical guides, we eventually adopted a Q&A format for our resulting report.
The A-part of the Q&A must present a clear conclusion, and we therefore first described the conclusion followed by detailed explanations. We also revised the contents according to the amendment of the GCP Ordinance, and obsolete Q&As were removed from the final report. Q&As were arranged in order of the related clause number of the GCP Ordinance, in accordance with the custom for other case examples, and were provided in an electronic medium that is easy to browse.
We wish our report will be helpful to individuals involved in clinical studies including auditees and new auditors.

Activity Summary of the 11th Term (April 2012 – March 2014)	
Special Project Group	Special Project Group 11
Theme	Construction of a System to Efficiently and Continuously Support Requests for Lectures Received by the GCP Division

(Summary)

Special Project Group 11 of the GCP division (C-T-11) began its activities in 2013, with the aim of achieving our task based on the theme in the title.

Specific purposes are listed below.

1) Aim to "create a system" that can appropriately respond to requests for lectures to the GCP Division of related Japanese and overseas organizations, and establish measures to achieve continuous operation and rapid effectiveness of the activities.
2) To clarify resources (lecture materials and lecturers) in the GCP Division, and examine their proper maintenance and a management system.
3) To closely examine the contents of the resources, and formulate consensus views on the requests to which they can be applied, whether they are usable or not, and whether it is necessary to revise them or not.
4) To select groups in the GCP Division for revision activities based on the results of examination of lecture materials, and perform activities under mutual understanding.
5) To select GCP Division members who are capable of giving lectures at outside organizations, and list them as lecturer candidates.
6) To systemically maintain resources that can respond to requests for lectures.

The activities during this term are as follows:

1) Legislation of internal rule.

We legislated the following internal rule on requests for lectures from outside organizations.

"Internal Rule 01 Response to Requests for Lectures/Lessons from Outside Organizations, Version 1.0, dated June 18, 2013."

2) We held the following lectures upon requests from outside organizations.

2) -1 Pharmaceutical and Medical Device Regulatory Science Society of Japan "Basic Training Course for Staff Engaged in Clinical Development of Pharmaceutical Drugs 2013."

- Title of lecture: GCP Inspections for Sponsors and Investigators/Institutions by Regulatory Agencies (PMDA, FDA).
  Lecturer: Yukio Fujino, Director of the GCP Division.
  Date: May 27, 2013.

- Title of Lecture: Quality Control and Quality Assurance of Clinical Trials
  - Audit and Monitoring -.
  Lecturer: Toru Hirai, Leader of C-T-11.
  Date: May 28, 2013.

2)-2 Japanese Society of Hospital Pharmacists "16th Workshop for CRC Training"

- Title of Lecture: GCP Audit for Investigators/Institutions by Sponsors.
  Lecturer: Toko Shimomukai, Member of C-T-11.
  Date: August 20, 2013.

2)-3 Yokohama City University Medical Department Graduate School, "Clinical Pharmacology course Fiscal Year 2013"

- Title of Lecture: Quality Control and Quality Assurance in Clinical Trials (1).
  Lecturer: Toru Hirai, Leader of C-2-A.
  Date: October 2, 2013.
- Title of Lecture: Quality Control and Quality Assurance in Clinical Trials (2).
  Lecturer: Yusuke Tsutsumi, Sub-Leader of C-2-C.
  Date: October 9, 2013.