Development of Cancer Cooperative Groups in Japan

Haruhiko Fukuda*

Japan Clinical Oncology Group Data Center, Clinical Trials and Practice Support Division, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan

*For reprints and all correspondence: Haruhiko Fukuda, Japan Clinical Oncology Group Data Center, Clinical Trials and Practice Support Division, Center for Cancer Control and Information Services, National Cancer Center, 104-0045 5-1-1 Tsukiji, Chuo-ku, Tokyo, Japan. E-mail: hrfukuda@ncc.go.jp

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Investigator-initiated clinical trials are essential for improving the standard of care for cancer patients, because pharmaceutical companies do not conduct trials that evaluate combination chemotherapy using drugs from different companies, surgery, radiotherapy or multimodal treatments. Government-sponsored cooperative groups have played a vital role in developing cancer therapeutics since the 1950s in the USA; however, the establishment of these groups in Japan did not take place until 30 years later. Methodological standards for multicenter cancer clinical trials were established in the 1980s by the National Cancer Institute and cooperative groups. The Japan Clinical Oncology Group, one of the largest cooperative groups in the country, was instituted in 1990. Its data center and operations office, formed during the 1990s, applied the standard methods of US cooperative groups. At present, the Japan Clinical Oncology Group consists of 14 subgroups, a Data Center, an Operations Office, nine standing committees and an Executive Committee represented by the Japan Clinical Oncology Group Chair. Quality control and quality assurance at the Japan Clinical Oncology Group, including regular central monitoring, statistical methods, interim analyses, adverse event reporting and site visit audit, have complied with international standards. Other cooperative groups have also been established in Japan since the 1980s; however, nobody figures out all of them. A project involving the restructuring of US cooperative groups has been ongoing since 2005. Learning from the success of this project will permit further progress of the cancer clinical trials enterprise in Japan.

Key words: clinical trials – cancer – therapeutic development – cooperative group

INTRODUCTION: UNIQUE FEATURES OF CANCER THERAPEUTIC DEVELOPMENT

In Japan, cancer has been the leading cause of death since 1981 and is accounting for 30% of all deaths (1). Currently, cancer is the most significant health problem facing the Japanese people. The recent 5-year survival rate for all cancers in Japan is still only 54%, and approximately half of cancer patients die within 5 years after their diagnosis (2). The development of anticancer therapies continues to pose a significant challenge.

Some types of cancer are curable with single-modality treatment, including surgery, radiotherapy or chemotherapy, e.g. surgery for early gastrointestinal cancer, radiotherapy for early head and neck cancer, and chemotherapy for child leukemia. However, most of the cancer patients need combined modality (multimodal) treatment for cure or for prolongation of survival, including therapies such as chemoradiation, adjuvant chemotherapy or radiotherapy before or after surgery. Advancement in chemotherapy can be achieved partly by the industry-sponsored clinical trials with the purpose of obtaining marketing approval of new anticancer agents (called ‘Chi-ken’ in Japanese). However, the development of combined modality treatments is not generally sponsored by pharmaceutical companies, making investigator-initiated clinical trials essential for the improvement of standard of care for cancer patients.

From an economical point of view, oncology drug development is not an attractive investment target for pharmaceutical industries. Oncology drugs account for only 2% of entire drug market in Japan. Additionally, the success rate of
oncology drug development, 5%, is very low, particularly when compared with other fields such as cardiovascular disease (20%) (3). The regulatory burden on pharmaceutical companies in the field of oncology, including, for instance, the National Cancer Institute (NCI), since the mid-1950s (4), as the NCI was solely responsible for the technology involved in anticancer drug development following the Second World War. The NCI established the Clinical Trials Cooperative Group Program to support cooperative groups in 1955 in their testing of the new anticancer agents developed by the NCI. Over five decades, the NCI has demonstrated strong leadership in cancer therapeutic development within the USA, not only with drugs but also with other modality treatments. One of its activities has been to support cooperative oncology groups. Although the proportion of government-sponsored Phase III cancer trials decreased in recent years compared with two decades ago (60%: 1975–84), one-third of trials are still sponsored by the government (31%: 1995–2004), whereas industry-sponsored Phase III trials increased to 57% (1995–2004) from 4% (1975–84) (5). Thus, in the USA, it is the government, specifically the NCI, that is the major sponsor of cancer clinical trials. On the contrary, in Japan, there has been no counterpart to the NCI, and it has therefore lagged ~30–40 years behind the USA in terms of cancer therapeutic development.

HISTORY OF THE US COOPERATIVE GROUPS

Understanding the history of cancer therapeutic development in the USA is of value, as it would inform us on how best to make up the delay described above. The first cancer-related randomized cooperative clinical trial was for acute leukemia (6). It was planned in 1954, begun in 1955, and reported in 1958 by Frei, Holland, Schneiderman et al. The trial compared two combination chemotherapy regimens (6-mercaptopurine and either intermittent or continuous methotrexate) in 65 patients, and it was conducted with a uniform protocol, a uniform criteria of response and random allocation of therapies. This trial was the initial model of current multicenter randomized clinical trials. The first randomized clinical trial in solid cancers was conducted by the Eastern Solid Tumor Group (currently, the Eastern Cooperative Oncology Group) and reported by Zubrod, Schneiderman et al. in 1960. The trial compared two alkylating agents (thiotepa versus nitrogen mustard) in patients with inoperative primary or metastatic solid tumors (breast, lung, melanoma and Hodgkin’s disease).

Following these successes, the NCI Clinical Trials Cooperative Group Program was conceived in 1955 and established 17 groups by 1958 (7). The initial aim of cooperative groups was to test new anticancer agents developed by the NCI, with their focus expanded in the mid-1960s to encompass the development of new disease-oriented combination chemotherapy regimens. Up to the early 1970s, most of patients who participated in clinical trials had advanced disease. Patients with early stage disease were included in larger numbers in the late 1970s. During the 1970s and 1980s, the emphasis of cooperative group trials was expanded again to evaluate combined modality treatments. Some of the initially established cooperative groups were small and disease-specific or regional, and through the 1960s and 1970s, such small groups were combined to nationwide multidisease groups (8). There were a total of 31 cooperative groups since 1955 to date, 14 of those remaining in 1979 and 10 remaining today. By the end of the 1970s, the configuration of the cooperative groups came to resemble their current style with each having its own large statistical center staffed by newly established professionals such as biostatisticians and data managers. In 1980–81, when the support mechanism for the Cooperative Group Program was converted from a grant to a cooperative agreement, the Cancer Therapy Evaluation Program (CTEP) in the NCI took on a considerable role in the oversight of cooperative groups, including trial concept selection, protocol review and approval, and oversight of trial operations (4).

The NCI-sponsored cooperative groups, which are called ‘Groups’, are currently comprised of four main types: (i) disease-oriented groups—GOG (Gynecologic Oncology Group) and NSABP (National Surgical Adjuvant Breast and Bowel Project); (ii) groups that focus on high-technology or single-modality studies—ACOSOG (American College of Surgeons Oncology Group), ACRIN (American College of Radiology Imaging Network) and RTOG (Radiation Therapy Oncology Group); (iii) groups in which investigators focus on a particular patient population—COG (Children’s Oncology Group); (iv) multidisciplinary national groups (called the ‘Big 4’)—CALGB (Cancer and Leukemia Group B), ECOG (Eastern Cooperative Oncology Group), NCCTG (North Central Cancer Treatment Group) and SWOG (Southwest Oncology Group) (4). Typically, cooperative groups’ statistical centers are associated with major university biostatistics departments, such as Duke University with...
CALGB, Harvard University with ECOG and the University of Washington with SWOG. Those universities have been acting as the major source of biostatisticians for their associated cooperative groups and as the source of knowledge regarding updated statistical methodology.

The current standard framework of clinical trials was established around 1960 by the NCI and the Cooperative Groups: Phase I trials are intended to identify a safe dosage, Phase II trials aim to determine where the agent or intervention has an effect on a particular cancer and Phase III trials have the goal of comparing the new agent or intervention (or new use of a treatment) with the current standard (9). During the 1970s, there were many controversies in the medical oncology community over the use of historical controls in clinical trials. However, in the 1980s, the concept of historically controlled screening studies followed by major randomized clinical trials seems to have become firmly established and accepted. Furthermore, in the late 1970s and early 1980s, several dynamic stratification methods for randomization were developed and became more widely used than conventional permuted block methods (static allocation methods) by the US cooperative groups and their European counterparts. The sample size calculation methods for Phase III cancer clinical trials that are in use at the present time were established in the 1980s by Rubinstein, by Bernstein and Lagakos, by Shoenfeld etc. Currently, popular sample size calculation methods for Phase II cancer clinical trials, such as Fleming’s one sample group sequential design, Simon’s two-stage design for one arm studies and Simon’s randomized selection design, were also developed in the 1980s (10).

The group sequential approach, which is a statistical term denoting procedures for interim analyses in Phase III randomized trials, was developed in the mid-1970s and was established in the 1980s. With this currently common method, interim analyses for early termination of the study are done at a limited number of pre-specified points during the course of a clinical trial (10). Up to the late 1970s, it was common practice to report annual or semi-annual interim outcome analyses of randomized studies to all investigators in Cooperative Groups. By the mid-1980s, demerits of this practice, which threaten the integrity of the study and reliability of the results, had become widely recognized, and dissemination of interim outcome reports became limited to a trial steering committee. Furthermore, in the 1990s under the leadership of the NCI, a data safety monitoring committee with a majority of members drawn from outside the cooperative group itself was assigned to review the interim analysis reports and to recommend whether a trial was to be continued or to be terminated early. This approach is now common worldwide (11).

Beyond 2000, methodological advances occurred in two major areas. One is the development of study design for the evaluation of targeted drugs using biomarkers, and the other is the international collaborative study framework. The details are discussed in excellent reviews by Sargent et al. (12), Mandrekar and Sargent (13) and Trimble et al. (14).

The situation regarding pediatric oncology group trials has many unique features when compared with the adult cancer trials. For example, 90–95% of US children with cancer participate in clinical trials, whereas only 3% of US adults with cancer participate in clinical trials (4,9). The scope of this manuscript is limited to the therapeutic development in adult cancer.

**DEVELOPMENT OF JAPANESE COOPERATIVE GROUPS**

*History repeats itself*

Karl Marx

The history of cancer clinical trials in Japan seems to follow that in the USA. Before the mid-1980s, there existed no investigator-initiated cancer cooperative groups as they are constituted today. Although small groups or informal consortiums conducted clinical researches on cancer therapy, most of this research consisted of retrospective studies, case series studies or industry-sponsored clinical trials. In the mid-1980, a couple of groups began investigator-initiated multi-institutional prospective clinical trials; however, they had no organized data coordinating center with statisticians and data managers. As was the case in the USA in the 1950s, study management procedures were undertaken by clinicians and their secretaries with insufficient knowledge of biostatistics and data management.

In the 1980s, Nagahiro Saijo, the second chair of the Japan Clinical Oncology Group (JCOG) and the first Japanese member of the Executive Committee of the American Society of Clinical Oncology (ASCO), along with other opinion leaders, aggressively introduced clinical trial methodology and cooperative group mechanisms being established in the USA and the Europe to the Japanese oncology community. And since around 1990, the concept and importance of clinical data management and statistical methodology in clinical trials have been recognized by the clinical oncology community thanks to tremendous efforts by Yasuo Ohashi, a leading statistician at the University of Tokyo. From the late 1980s through the early 1990s, the leaders of spontaneously forming research groups became aware of the importance of data coordinating centers that are continuously organized by statisticians and data managers, and several groups established centers capable of central patient registration and central randomization with full-time data managers. This turning point occurred in Japan at least 30 years after it took place in the USA.

Through the 1990s, the coordinating centers of such groups had been gradually organized to increase the quality and quantity of clinical trials; however, they were continuously unstable and administratively fragile, especially in their hiring practices. The governmental research funds had many limitations in hiring people, such as inability to guarantee social security and health insurance, a low upper salary limit and no commuting allowance. These restrictions
posed significant hurdles to hiring new experts on clinical trials and retaining existing ones, especially data managers. Since 2000, most of the groups had established the corporate entity, i.e. non-profit organizations, within the group or by the group as a whole. To date, each major cooperative group in Japan has its own corporate entity and hires peoples in a stable manner even though the stability of administrations is insufficient and varies in their affiliation or parent organization by groups.

Methodological advancement has been accomplished in cooperative groups in Japan by introducing US and European approaches to managing multicenter cancer clinical trials. It is currently thought that Japan lags behind Western countries by 10 years in terms of methodological development. For example, interim analysis reports had been opened to steering committees in Japan annually or semi-annually before the mid-1990s; however, excluding participating investigators from a data and safety monitoring committee review as is the current worldwide standard occurred only in the late 1990s. At this point, most of the statistical methods used in Japanese cooperative groups are identical to those used by their US and European counterparts.

**History of Organizing JCOG: An Example**

*Ontogeny recapitulates phylogeny*

Ernst Heinrich Philipp August Haeckel

Recapitulation theory holds that the growth and development of an individual organism copies the evolutionary history of the species (Wikipedia). The developmental process of an individual cooperative group seems to copy the history of the methodological advancement of the entire clinical trials enterprise. Therefore, reviewing the history of a specific cooperative group and/or data coordinating center is considered to be of help in understanding the principle of clinical trials as well as methodological and organizational advancement. The history of JCOG is one example of the formation of a cooperative group structure and coordinating center, and it can be used a model by an individual who desires to establish his or her own clinical trial organization.

**Pioneering Days and Forming Disease-oriented Subgroups**

The initial research grant forming the basis of JCOG was secured in 1978 (15) and entitled ‘A study on the Multidisciplinary Treatment for Cancer’. The project, chaired by Keiichi Suemasu, was supported by a Grant-in-Aid for Cancer Research from the Ministry of Health and Welfare (currently, the Ministry of Health, Labour and Welfare). The Lymphoma Study Group (LSG) chaired by Masanori Shimoyama, and the Japan Esophageal Oncology Group (JEOG) chaired by Norifumi Iizuka, started the group’s research activity at that time. Subsequently, the Lung Cancer Study Group (LCSG) was formed and chaired by Nagahiro Saijo in 1982, the Gastric Cancer Surgical Study Group (GCSSG) by Toshifusa Nakajima in 1984, the Gastrointestinal Oncology Study Group (GIOSG) by Minoru Kurihara, the Breast Cancer Study Group by Kaoru Abe in 1985 and the Lung Cancer Surgical Study Group (LCSSG) by Mitsuo Ohta in 1986 joined the research group project. The LCSG had two subgroups, East Japan LCSG (EJ-LCSG) and West Japan LCSG (WJ-LCSG), with the latter developing eventually into the current West Japan Oncology Group later. Each disease-oriented subgroup produced its own study protocol, conducted the study, analyzed data and published results; however, for the most part, these groups performed these activities independently from one another and there was no peer-review system encompassing the research group as a whole.

**Organizing of Committees**

Since 1988, the grant project was chaired by Masanori Shimoyama with a different title—‘A study on the Multidisciplinary Treatment for Solid Cancer’. In 1985, under the leadership of Shimoyama, the investigators established the Constitutions and Bylaws for research activities, two core committees, the Clinical Trials Review Committee (CTRC, current Protocol Review Committee) and the Independent Monitoring Committee (IMC, current Data and Safety Monitoring Committee), and the Scientific and Ethical Guidelines for this grant-based research group. Since then, all research protocols have been reviewed and approved by the CTRC before being submitted to the institutional review board of each participating institution, and all ongoing studies have been monitored through the review of monitoring reports every 6 months by the IMC. Because the members of these two core committees consisted of the chairpersons of each subgroup or the key investigators within subgroups, these committees were not ‘independent’; however, this peer-review system has been working well to improve the quality of the studies from scientific and ethical perspectives over the past two decades. The joint committee meetings by the CTRC and the IMC were held semi-annually and functioned in a decision-making capacity regarding all research activity. The joint committee was named the Steering Committee in 1987 and began meeting every 3 months, then was renamed the Executive Committee in 2000.

**Naming of JCOG and Establishment of JCOG Statistical Center**

Before 1989, study protocols and trial data had been managed by investigators themselves (physicians or surgeons) and their secretaries. A small statistics section was set up in 1989 by Shimoyama within the National Cancer Center Hospital, and the study data were gathered into this statistics section at that time. In 1990, the grant-based research group was named the JCOG by the Steering Committee, and the statistical section was named the JCOG Statistical Center. The first JCOG Chair was Masanori Shimoyama.
The JCOG Statistical Center was also directed by Shimoyama and began central patient registration and randomization using the minimization method. Since then, new-comers to JCOG have joined one by one—the Gynecologic Cancer Study Group (GCSG), chaired by Ryuichiro Tsunematsu, in 1995; the Colorectal Cancer Study Group (CCSG), chaired by Yoshihiro Moriya, and the Urologic Oncology Group (UOSG), chaired by Kenichi Tobisu, in 2001; the Bone and Soft Tissue Tumor Study Group (BSTTSG), chaired by Yuukihide Iwamoto, in 2002; the Radiation Therapy Study Group (RTSG), chaired by Masahiro Hiraoka, and the Brain Tumor Study Group (BTSG), chaired by Kazuhiro Nomura, in 2003; and finally the Hepatobiliary and Pancreatic Oncology Group (HBPOG), chaired by Junji Furuse, joined JCOG in 2008. The subgroup structure has remained the same since. The current organizational structure is shown in Fig. 1 and the list of the subgroups and their chairpersons are shown in Table 1.

The JCOG Statistical Center was relocated to the National Cancer Center Research Institute East, Kashiwa, Chiba, between 1995 and 1996. The Director of the Statistical Center at that time had been Shoichiro Tsugane, Chief of the Epidemiology and Biostatistics Division. In these early days, human resources were quite limited. Three to four staff members including the Director (who was not affiliated full-time) were assigned to JCOG. The research associates and secretaries with time wages managed all trial-related jobs, such as patient registration including randomization, collecting case report forms, entering data into the database, processing semi-annual monitoring reports and roster management, for more than 30 ongoing trials and around 20 trials in follow-up. As a logical consequence, data quality and reporting of problems and safety issues to investigators was far from satisfactory.

REORGANIZING JCOG STATISTICAL CENTER INTO JCOG DATA CENTER

The Statistical Center was relocated again to the National Cancer Center Research Institute East, Tsukiji, Tokyo, in 1996 and came under the direction of Naohito Yamaguchi, Chief of the Cancer Information and Epidemiology Division. Kaoru Abe, the President of National Cancer Center at that time assigned Haruhiko Fukuda to reorganize the Statistical Center. At the time of relocation to Tsukiji, the JCOG Statistical Center managed 37 trials open for accrual and 22 trials in follow-up. Reorganization was started with the separation of the Data Management and Statistics sections as well as specification of shared responsibilities. In the early days, the data management section was composed of three data managers and an assistant, and the statistics section was composed of six staff members (statisticians and epidemiologists) in the Cancer Information and Epidemiology Division, each assigned part-time to one or two subgroups. Reorganizing efforts included prohibiting the registration of ineligible patients, reminding site investigators about unsubmitted case report forms, querying missing data and logical inconsistency, changing the language of reports from English to Japanese and compiling list of ineligible cases, protocol deviations and serious adverse events along with the names of relevant institutions. This type of feedback to the site investigators was believed to be critical in improving and maintaining the quality of data and study management, which would in turn help ensure the scientific integrity of trial results and minimize the risk of enrolled patients. The JCOG Statistical Center was renamed the JCOG Data Center in 1998, with the intent of spreading understanding of the

Table 1. JCOG subgroups and chairs in JCOG at 2010

<table>
<thead>
<tr>
<th>Name</th>
<th>Chair</th>
<th>Year subgroup established</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma Study Group</td>
<td>Kunihiro Tsukasaki</td>
<td>1978</td>
</tr>
<tr>
<td>Japan Esophageal Oncology Group</td>
<td>Nobutoshi Ando</td>
<td>1978</td>
</tr>
<tr>
<td>Lung Cancer Study Group</td>
<td>Tomohide Tamura</td>
<td>1982</td>
</tr>
<tr>
<td>Gastric Cancer Surgical Study Group</td>
<td>Mitsuru Sasaki</td>
<td>1984</td>
</tr>
<tr>
<td>Gastrointestinal Oncology Study Group</td>
<td>Narikazu Boku</td>
<td>1985</td>
</tr>
<tr>
<td>Breast Cancer Study Group</td>
<td>Hiroi Iwata</td>
<td>1985</td>
</tr>
<tr>
<td>Lung Cancer Surgical Study Group</td>
<td>Masahiro Tsuboi</td>
<td>1986</td>
</tr>
<tr>
<td>Gynecologic Cancer Study Group</td>
<td>Toshiharu Kamura</td>
<td>1995</td>
</tr>
<tr>
<td>Colorectal Cancer Study Group</td>
<td>Yoshihiro Moriya</td>
<td>2001</td>
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<tr>
<td>Urologic Oncology Study Group</td>
<td>Kenichi Tobisu</td>
<td>2001</td>
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<tr>
<td>Bone and Soft Tissue Tumor Study Group</td>
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<tr>
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<td>Masahiro Hiraoka</td>
<td>2003</td>
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<tr>
<td>Brain Tumor Study Group</td>
<td>Soichiro Shibui</td>
<td>2003</td>
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<tr>
<td>Hepatobiliary and Pancreatic Oncology Group</td>
<td>Junji Furuse</td>
<td>2008</td>
</tr>
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Figure 1. Organizational structure of JCOG.
Development of cancer cooperative groups in Japan

**Phase III randomized trials before 1996, and the alpha multiplicity had been performed in the interim analysis of**

**ment works than in statistical jobs, not only in JCOG but data coordinating centers is much greater in data management, education and project management), and two sections in the Operations Office, the Study Coordinating Section and the Quality Assurance Section (audit, DSMC office).**

**COLLABORATION WITH THE SOCIETY OF JAPANESE PHARMACOPOEIA AND ESTABLISHMENT OF NPO-CORE**

Because the number of employees in the National Cancer Center was limited by governmental regulations, the establishment of an organization, such as data coordinating center, composed of newly recognized experts was quite difficult. Persons who intended to found such organizations (including but not limited to the JCOG) were forced to seek pathways that did not create new sections within the National Centers. In 2001, the Data Management Promotion project grant was offered by the Ministry of Health, Labour and Welfare as a supplement to the Health and Labour Sciences Research Grants for the 21st Century Medical Frontier Research. The Society of Japanese Pharmacopoeia (SJP, Nihon-Kouteisyo-Kyokai, currently Pharmaceutical and Medical Device Regulatory Science Society of Japan: PMRJ) established two academic data coordinating centers for clinical trials based on this grant. One was located in the National Center for Global Health and Medicine for lifestyle-related disease trials, and the other was located in the National Cancer Center for cancer clinical trials. The data coordinating center of the latter had been managed in collaboration with the Cancer Information and Epidemiology Division and virtually acting as the JCOG Data Center.

The collaboration with SJP Foundation since 2001 contributed greatly to improving the JCOG Data Center qualitatively and quantitatively. The number of staff increased from 15 to 30 over 5 years, and SJP employees received health insurance, social security and a commuting allowance by the Foundation. Unfortunately, however, the Data Management Promotion project unexpectedly expired in 2006 due to changes in governmental policy regarding the management of foundations. To maintain staff employment, a non-profit organization, the Clinical Oncology Research and Education (NPO-CORE), was established in 2006, and staff were transferred into NPO-CORE between 2006 and 2007. Since then, the JCOG Data Center and JCOG Operations Office have been administered based on the contract between NPO-CORE and the newly established Clinical Trials and Practice Support Division of the Center for Cancer Control and Information Services within the National Cancer Center.

Masanori Shimoyama, the original JCOG Chair, was succeeded by the second JCOG Chair, Nagahiro Saijo, in 2001, who in turn was followed by the third JCOG Chair, Tomohide Tamura, in 2009. The Director of the JCOG Data Center has been Haruhiko Fukuda since 1999, and the Director of the JCOG Operations Office has been Kenichi Nakamura since 2008. The core research grant for JCOG, ‘A study on the Multidisciplinary Treatment for Solid Cancer (8S-1)’, was divided into four grants to intensify research activity in 1999. These grants were: 11S-1 for **importance of data management. In fact, the workload in data coordinating centers is much greater in data management works than in statistical jobs, not only in JCOG but also in cooperative groups worldwide.**

**Several revisions in statistical methodology were also conducted during this period. No formal adjustment for multiplicity had been performed in the interim analysis of Phase III randomized trials before 1996, and the alpha spending function method with O’Brien and Fleming boundary (16) was introduced as a de facto standard in 1997. The adjustment based on the Southwest Oncology Group (general affairs, accounting, labor management, roster management, education and project management), and two sections in the Operations Office, the Study Coordinating Section and the Quality Assurance Section (audit, DSMC office).**

The first-generation database system, the JCOG DB system, in the Statistical Center was constructed using relational database software system G-BASE (Richo Co., Ltd). This was done as part of a Grant-in-Aid for Basic Research from the Science and Technology Agency between 1991 and 1993 (17). The maintenance and reform of the database system was supported afterward by a Grant-in-Aid for Second Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labour and Welfare. The first-generation JCOGDB system used UNIX as its operating system and was highly standardized across all diseases and treatment modalities. All tables could be processed and printed out in the same styles across studies; however, Japanese word-processing functionality was quite limited in those days and the system could not efficiently handle Japanese characters. These limitations resulted in difficulties with detailed reporting and feedback of problems to the investigators. The first-generation system was replaced between 1997 and 1999 by a second-generation JCOGDB system designed and constructed by customizing EDMS, a commercial clinical data management system software package by EPS Co., Ltd. The JCOG Data Center is currently using this second DB system and makes continued efforts to maintain and improve it via revisions and updates. Since the system enabled web-based patient registration in 2009, all trials initiated since 2010 are capable of enrolling subjects in this way.

**The efforts mentioned above were performed in parallel with increasing the number of staff in data management and in other sections that were established one by one. The JCOG Data Center was composed of 10 members in 1998. The Computing Section, which administers hardware, software and computer networks, was created in 1998, whereas the Medical Section (currently, the Study Coordinating Section in the Operations Office) which supports drafting of protocols and publications was set up in 2002. In 2006, the Data Center and the Committee Office were reorganized into four Data Center sections, namely Data Management, Statistics, Computing Sections and the Office of the Director (general affairs, accounting, labor management, roster management, education and project management), and two sections in the Operations Office, the Study Coordinating Section and the Quality Assurance Section (audit, DSMC office).**

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chemosensitive cancers (lymphoma, breast, gynecology),
headed by Tomomitsu Hotta; 11S-2 for lung cancer, chaired
by Nagahiro Saijo; 11S-3 for gastrointestinal cancers,
headed by Shigeaki Yoshida; and 11S-4 for data center and
committees by Masanori Shimoyama. These core grants
have been successful to date, with minor modifications.
These four core grants were divided into five grants in
2005, and again divided into six grants in 2008. Currently,
six core grants support the fundamental activity of JCOG:
20S-1 for chemosensitive cancers, chaired by Kensei
Tobinai; 20S-2 for lung cancer, chaired by Tomohide Tamura;
20S-3 for gastrointestinal, hepatobiliary and pan-
creatic cancers, chaired by Yasuhiro Shimada; 20S-4 for rare
cancers (brain, bone and soft tissue, urology), chaired by
Soichiro Shibui; 20S-5 for radiotherapy, chaired by
Masahiro Hiraoka; and 20S-6 for committees, chaired by
Haruhiko Fukuda.

**Expansion of Quality Control and Quality Assurance**

Adverse event reporting is extremely important in reducing
risk to patients enrolled in clinical trials, especially in multi-
center cancer clinical trials. ‘Expected’ adverse events,
which are defined as being described in the protocol or in
the package insert, are the adverse events that the participat-
ing investigators know how to treat. Conversely, the investi-
gators may not know how to treat patients when ‘unexpected’ adverse events arise, and sharing information
about such adverse events among investigators would be of
help in reducing patient risk. In single-institution trials,
sharing such information should be done easily and spon-
taneously during routine clinical practice and via
non-document-based communication; however, in multici-
ter clinical trials, such information can be shared only by
exchanging documents. Thus, the information regarding an
unexpected adverse event that occurs at a specific participat-
ing site should be shared among investigators in a timely
manner to most effectively minimize patient risk.

The first guideline for Adverse Event Reporting in JCOG
was formalized in 1985 when the IMC was organized.
However, there were very few adverse event reports sub-
mitted to the IMC in compliance with the guidelines until
1996. The number of adverse event reports increased from
less than 10 to more than 30 per year between 1997 and
2000, when the current style of monitoring reports and the
site visit auditing system were established. Minimizing risk
to enrolled patients cannot be realized in the absence of a
functional quality control system. The current Adverse Event
Reporting system in JCOG is compatible with the guidelines
issued by the International Conference of Harmonization
(ICH), ‘E2A: Clinical Safety Data Management: Definitions
and Standards for Expedited Reporting’ and ‘E2D:
Post-Approval Safety Data Management: Definitions and
Standards for Expedited Reporting’ (18).

The JCOG site visit audit was conceived in 1999 and
begun in 2000 in compliance with the Monitoring

Guidelines implemented at that time by the Clinical Trials
Monitoring Branch of the CTEP, NCI (now revised and
expanded to include central registration by the Cancer Trials
Support Unit) (19). The site visits have been performed on a
monthly basis, usually totaling 10 visits per year. A 3-year
auditing cycle is used, but only one-fourth to one-third of
participating hospitals in JCOG have been audited during
each cycle due to the insufficient human resources. The
current cycle began in January 2009, and the frequency and
total number of site visit will hopefully grow within this
cycle or the next as a result of increasing the number of
staff.

A protocol manual was drafted by JCOG in 1999 and for-
malized in 2001 for the streamlining of protocol develop-
ment and for increasing the scientific quality of protocol
documents. This provides a standardized chapter structure,
instructions on how to write the protocol sections, and tem-
plate documents required by JCOG policies and being com-
pliant with the ethical guidelines. Streamlining of protocol
development has been one of the major concerns not only in
JCOG but also in the Western cooperative groups. Dilts
et al. reported that median calendar days to activate a Phase
III trial are 784 in CALGB (20) and 808 in ECOG (21).
According to the preliminary data analysis in JCOG, the
median days to activate all JCOG protocols that were
approved between 2000 and 2009 were 565. Detailed data
analyzes and the protocol streamlining project within JCOG
are ongoing. The project includes making chapter structure
of ‘Background’ identical between the protocol concept and
full protocol, bringing transparency to the progress of proto-
col drafting for all JCOG investigators via a members-only
site in the JCOG website monthly. It also involves establish-
ing the new position of a protocol manager, a non-physician
writing professional who supports physician protocol coordi-
nators, and acts as a project manager and a time-keeper in
protocol drafting.

**The Other Cooperative Groups in Japan**

A brief introduction to the other cancer cooperative groups is
given here. The Japanese cooperative groups, that two or
more their Phase III trials are registered at the UMIN
Clinical Trials Registry (http://www.umin.ac.jp/ctr/index-j.
htm) as of March 2010 and group information is available at
their websites, are nominated. The material in this section
comes mainly from group websites, supplemented by per-
sonal communication.

**Multidisease Groups**

**West Japan Oncology Group:** [http://www.wjog.org/].
West Japan Oncology Group (WJOG) was formerly known as the
expert group specific to lung cancer, but now is active as a
multidisease group chaired by Yoichi Nakaniishi. It was
named the West Japan Lung Cancer Group (WJLCG) in
1992 and renamed the West Japan Thoracic Oncology Group
(WJTOG) in 1997. Its data center was initially set up at Kinki University in 1998 and initiated central patient registration. The NPO-WJTOG was established in 2000 and established a new independent office in Namba, Osaka, in 2004. The Gastro-intestinal Group was established in 2007 within the group and became a multidisease group, and was renamed the WJOJ. WJOJ and JCOG are now conducting three intergroup trials for lung cancer: JCOG0802/WJOG4607L—randomized Phase III trial comparing lobectomy and limited surgery for non-small cell lung cancer; JCOG0803/WJOG4307L—randomized Phase III trial evaluating chemotherapy for elderly patients with non-small cell lung cancer; and JCOG0804/WJOG4507L—Phase II trial evaluating limited surgery for early non-small cell lung cancer. The Director of the WJOJ Data Center is Shinichiro Nakamura.

**Japanese Foundation for Multidisciplinary Treatment of Cancer:** [http://www.jfmc.or.jp/](http://www.jfmc.or.jp/). Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC) is a long-standing group that was established in 1980 and is chaired by Shigetoyo Saji. It is famous for adjuvant trials for gastric cancers and colorectal cancers and has conducted some leukemia studies. In the early 1990s, JFMC established its own quality control system, called Project Coordinating System, that depended on close communication among site investigators, local data managers and the study chairs. Recently, it has expanded its activity to health service research including evaluation of palliative therapy and in-home patient care. The Foundation also uses its funding mechanism to act as a sponsor of research conducted outside of JFMC. The Director of the JFMC Data Center is Hiroaki Nakazato.

**The Japan-multinational Trial Organization:** [http://www.jmto.org/](http://www.jmto.org/). On the basis of an international communication program called ‘the US Japan Clinical Trial Summit Meeting’ that occurred between the SWOG and Japanese researchers since 1992, lead by Masanori Fukushima and Charles Coltman Jr., the Japan-multinational Trial Organization (JMTO) was established as a research group in 1999. It conducted ‘common-arm’ trials for lung cancer between SWOG and JMTO. Although it has since focused mainly on lung cancer, it recently conducted trials for ovarian cancer, breast cancer and colorectal cancer. JMTO is chaired by Hiromi Wada.

**Disease-specific groups**

**Japanese Adult Leukemia Study Group:** [http://www.jalsg.jp/](http://www.jalsg.jp/). Japan Adult Leukemia Study Group (JALSG) is a disease-specific group that has focused on adult leukemia studies. It was established in 1987 and is chaired by Tomoki Naoe. It has been partly funded by a Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare and was reorganized into a non-profit organization, NPO-JALS, in 2006. JALSG has conducted clinical trials for adult acute myeloid and lymphoid leukemia and chronic myeloid leukemia, as well as a large-scale cohort study for acute myeloid leukemia and myelodysplastic syndrome.

**Japanese Gynecologic Oncology Group:** [http://www.jgog.gr.jp/](http://www.jgog.gr.jp/). Japanese Gynecologic Oncology Group (JGOG) is a disease-specific group that concentrates on gynecologic malignancy, ovarian cancer, uterine cancer and cervical cancer. It was established in 2003 and is chaired by Kazunori Ochiai. Its NPO body was established in 2002. Of note, JGOG is a pioneer among other Japanese cooperative groups in terms of international collaboration. GOG-Japan, which is the subset of JGOG member institutions that have high-volume centers having the Federalwide Assurance from the US government, is conducting an international collaborative study with the US Gynecologic Oncology Group. The Director of the JGOG Data Center is Masahiro Takeuchi.

**National Surgical Adjuvant Study of Breast Cancer:** [http://www.csp.or.jp/cspor/](http://www.csp.or.jp/cspor/). National Surgical Adjuvant Study of Breast Cancer (N-SASBC) is a group that focuses on breast cancer, primarily on surgical adjuvant trials. N-SASBC was initially a component of contracted projects for pharmacoepidemiology research by the Ministry of Health and Welfare in 1996. After the expiration of the contracted projects in 2000, the group’s activities were succeeded by the Comprehensive Support Project for Oncology Research (CSPOR) of the Public Health Research Foundation (http://www.phrf.jp/). The data coordinating center is commissioned to the NPO-Japan Clinical Research Support Unit (J-CRSU) (http://www.crsu.org/). N-SASBC has also focused on the health outcome research including patient-reported quality-of-life assessment.

Japan contains many research groups besides those listed above that are domestic and/or specific to single diseases; however, their number and organizational structure are unknown because the country does not have a system that oversees cooperative groups.

**Restructuring of the clinical trials enterprise in the USA**

The clinical trial system in the USA seems highly developed in comparison with that in Japan; however, the US Cooperative Group enterprise has been undergoing restructuring since 2005 after its initial 50 years of existence. Although the US Cooperative Groups are recognized as having made great contributions to the field of cancer therapeutics over the past five decades, many stakeholders in the clinical oncology community have come to believe that the cooperative group system is increasingly inefficient, marked
by significant and unnecessary duplication of efforts and wasting of limited resources (4).

In 1996, the NCI director and the chair of the Extramural Board of Scientific Advisors commissioned an external review of the Cooperative Group Program by the Clinical Trials Review Group. The report of this group, released in 1997, is known as ‘the Armitage report’. It contained recommendations regarding the review, funding, design, oversight and administration of the NCI clinical trials system (22). In 2004, based on the Armitage report, the NCI director established the Clinical Trials Working Group (CTWG) to develop recommendations to (i) optimize the NCI-supported clinical trials system by improving coordination and research infrastructure, (ii) remove institutional and regulatory barriers that inhibit collaboration in clinical trials research and (iii) envision the ways in which clinical trials can use the tools of contemporary bioinformatics and molecular medicine. The committee released its findings in 2005. They included 22 recommendations to achieve four major goals: (i) better coordination, (ii) prioritization based on solid science and the needs of patients, (iii) standardized tools and procedures, and (iv) improved operational efficiency (23).

The recommendations included consolidating current cooperative groups (reducing their number), and the likely merging of groups focused on a single disease site or modality with multidisciplinary groups. The streamlining of protocol development was also emphasized. The deadline for final protocol approval after initial submission to the NCI was set at 300 workdays for Phase III trials and 210 days for Phase II trials. Trials that fail to open and accrue patients within 18 calendar months for Phase II or 2 years for Phase III are to be eliminated. A peer-review system of trial concepts was proposed, in which the group reviews and scores concepts each other, the groups are then ranked based on the score obtained through the peer-review process, and the group with higher rank receives the higher priority in obtaining NCI assistance with their trials. Increasing the per-case reimbursement rate (currently, 2000 US dollars per patient) was also recommended.

The NCI has launched several initiatives in response to the CTWG report. These include establishing a several new committees: the Clinical Trials Advisory Committee (CTAC), which is both extramural and intramural to the NCI; the Clinical Trials and Translational Research Operations Committee (CTROC), as an internal NCI advisory committee responsible for review of ongoing clinical trials and prioritization of proposed NCI-supported clinical trials, correlative science programs and translational research; and the Investigational Drug Steering Committee (IDSC) to improve the prioritization and scientific quality of clinical trials. The Coordinating Center for Clinical Trials was also established to oversee the implementation of the initiatives recommended by the CTWG. The process of concept review will emphasize early identification of all issues and resolving fundamental aspects of study design at protocol concept stage.

**CAN WE LEARN FROM THE RESTRUCTURING IN THE USA?**

Of the various recommendations and actions mentioned above, only some are applicable to the Japanese cooperative group enterprise, because there is no counterpart to CTEP and the Clinical Trials Cooperative Group Program and no reimbursement system per patient available in Japan. However, proposals such as peer review and a scoring system for trial concepts and a deadline for activating protocols may be introduced within each individual cooperative group. Additionally, many small, domestic, single-disease groups may be consolidated into a lower number of larger, multidisease groups in the next couple of coming decades in Japan as is occurring in the USA.

In broad terms, there seems to be two major possible future frameworks in Japan. One would involve the National Cancer Center or an alternative agency constructing a governing system like CTEP, which would control and support existing cooperative groups and early development research groups led by university hospitals or domestic cancer centers. The other would require existing cooperative groups to harmonize and collaborate with each other in a voluntary manner. The former framework would be efficient and powerful with regard to prioritization of trials and promotion of standardization; however, it would necessitate strong leadership and significant human resource allocation by the National Cancer Center or another agency. This is not considered realistic within the current economic situation in Japan, and it is difficult to envision whether a top-down decision-making scheme would suit the Japanese cultural way of thinking. The latter approach may not be powerful or efficient; however, it would be easy to start. As an example, a pilot project involving communication among the coordinating centers of existing Japanese cooperative groups is already ongoing. Participating groups include JALSG, JCOG, J-CRSU, JGOG, WJOG and JPLSG (Japanese Pediatric Leukemia/Lymphoma Study Group). The project is based on research grant 20S-6, chaired by Haruhiko Fukuda, which is part of a Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare. Research grant 20S-7, chaired by Atsushi Ohtsu, is also trying to harmonize research activities in the fields of lung cancer and gastric cancer between large-scale multidisease groups conducting mainly Phase III trials and domestic small groups conducting mainly Phase II trials. Hopefully, these groups will hold a strategic meeting soon to further collaboration and to implement efficient role sharing.

The goals and perspectives of cancer cooperative groups are similar worldwide, producing valuable and reliable evidence for the improvement of therapy for cancer patients as rapidly as possible. All efforts should be dedicated to achieving these goals by increasing the scientific and ethical quality of studies and by streamlining protocol development and study completion. All those who promote the development of anticancer therapeutics should not hesitate to learn from Western countries and each other.
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Conflict of interest statement

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