Based on the three philosophies expressed above, we have developed our efforts focusing around the medical center, research and education. In 2004 Kyoto University became a national university corporation which required an increase in management efforts as well as of streamlining the management. At the same time, there has been increased effort to strengthen cooperation with medical institutions in the region, and in 2005, we launched Kyoto University Hospital Integrated Clinical Education Center, which focuses on the education and training of not only physicians and dentists but also of pharmacists and medical staff.

A Core Clinical Research Hospital to provide world class advanced medical care

We strongly believe we can create a world class medical hub of core clinical research at Kyoto University through orchestrating protocol development (social medicine) centered around clinical epidemiology, high quality research plans (basic science), and clinical research support (clinical medicine). Furthermore, Kyoto University is poised to answer to the needs of researchers from all over the country by securing the international ICH-GCP compliant status, building up ability in research planning that will anticipate commercialization potential with reliable technology transfer and intellectual property management. Along with infrastructure development, we would like to build a network that includes collaboration and serves as a base for clinical research. This will help us contribute to the rapid progress of medical innovation in Japan, as well as create world class evidence-based medicine. We aim to provide advance treatments as early as possible to those suffering from incurable diseases.

To promote clinical research on international standards and place Japanese medical care at the forefront

In 2012, Kyoto University Hospital was selected as one of the five designated “Core Clinical Research Hospitals” by the Ministry of Health, Labour and Welfare. Core Clinical Research Hospital implies that the organization is linked to other medical institutions through a network in which it itself plays a central role. In response to this designation, the “Kyoto University Hospital Core Clinical Research Hospitals Initiative” was assessed, and each organization such as the Translational Research Center, the Clinical Trial Control Center, EBM Research Center and the Department of R&D and Corporate Integration has been integrated into one organization and made a fresh start from April 2013 as the “Institute for Advancement of Clinical and Translational Science (iACT)”. Originally in Japan there was excellent basic research from medical colleges and research centers as well development research from companies with worldwide reputation. Despite this, it is thought that one of the reasons for the big gap between Japan and western countries in advanced medical development is that for a long time there has been no system in place in Japan that was conducive to the clinical application of medical research. iACT will work as an incubator to generate novel medical devices and drugs through validation of results of day-to-day medical examination or treatment with improvements through re-evaluation of current treatments. In other words, iACT will create a clinical research team of international standards in drug discovery, which will include doctors, and teams of specialized coordinators, patient's physicians, data management personnel and statisticians. More specifically, in the short period of the next 5 to 10 years we aim to develop drugs for intractable diseases through completely novel concepts.

Deputy Director of Kyoto University Hospital

Shinji Uemoto

Director of Institute for Advancement of Clinical and Translational Science (iACT)

Michiaki Mishima

Kyoto University Executive Director (Executive Vice-President for International Affairs and Hospital Administration), Director of Kyoto University Hospital

Basic Principals

1. Providing safe and highquality medical care as a patient-centered hospital
2. Contributing to society through the development and practice of new treatments
3. Fostering medical professionals with a sense of mission, and responsibility as well as compassion

Declaration of the Rights of Patients

We will respect the rights of patients based on the philosophy and medical ethics of this hospital

1. Right to receive good medical care while maintaining the dignity of the person
2. Right to receive sufficient information and explanation, in order to make decisions regarding treatment options
3. Right to privacy protection

History

1899  Establishment of Kyoto Imperial University College of Medicine
1899  Opening of Kyoto Imperial University College of Medicine Hospital
1919  Renaming of Kyoto Imperial University Hospital
1949  Renaming of Kyoto University Hospital
1998  Merging of Chest Disease Research Institute (160 beds)
2004  All of Japan’s national universities became independent corporations
2007  Establishment of Kyoto University Cancer Center
2011  Establishment of Clinical Research Center for Medical Equipment Development
2013  Establishment of the Institute for Advancement of Clinical and Translational Science (iACT)
Kyoto University Hospital was selected as a "Core Clinical Research Hospital" in the year 2012 by the Ministry of Health Labour and Welfare. This designation of Core Clinical Research Hospital involves core clinical development projects which play a central role in investigator-initiated IND/IDE trials for intractable diseases and high quality clinical research as well as post-marketing research for development of innovative medical drugs and devices that are first of its kind in Japan. Based on this selection, and in order to address the objective of promotion of clinical trial networks, iACT has decided not to limit itself to sponsor-initiated clinical trials. Thus it aims to extend support in all matters related to investigator-initiated IND/IDE trials, monitoring and execution of clinical trials through collaboration, information exchange, personnel support training in order to carry out high quality clinical research within the network.

**History**

- 1999: Establishment of clinical trial management center (within the hospital)
- 2001: Establishment of the Graduate School of Medicine EBM collaborative center
- 2002: Department of Clinical Innovative Medicine
- 2003: Formed the Department of Epidemiological & Clinical Research Information Management (by September 2006)
- 2007: Name of Graduate School of Medicine EBM collaborative research center changed to EBM research center
- 2008: Research support of drug discovery by "cell –cell signaling control that target intractable diseases in the "Biomedical Research and Innovation Zone (super-zone)"
- 2009: Establishment of the EBM research project by Sep 2011
- 2012: Translational Research Network Program (Second Stage) funded by Ministry of Education, Culture, Sports, Science and Technology (MEXT)
- 2013: Founding of the Institute for Advancement of Clinical and Translational Science (iACT)

Clinical research support system at Kyoto University
Based on the research outcomes of Kyoto University Life Sciences (Kyoto University Hospital), the Department of R&D Alliances that launched as Department of R&D and Corporate Integration in April 2004 has been specializing in activities such as industry academia-partnership, intellectual property management and “use of the rights” following the acquisition of rights. In particular we are working in the following four areas:

1. “Seek and Develop Research Proposals” which means to elicit unused technologies or patents and increase clinical research proposals by acting as a liaison office for receiving and managing such proposals from within and outside of the university
2. “Intellectual Property Management” through intellectual property related consultation that extends from before and after patent application with the aim of commercialization potential and maximizing intellectual property value based on the qualitative improvement and to increase the quantity of intellectual property
3. “Negotiation and Contract” in order to build cooperation network with universities and companies within Japan and overseas and to support the matching of corporate needs with clinical research proposals from universities
4. “International Cooperation” which facilitates participation in industry, government, academic collaborative activities and international cooperation activities of Kyoto University Life Sciences.

Through the activities in these four areas, we aim to support seamless technology transfer through seeking out clinical research proposals, patent application, corporate negotiations, contracts as well as commercialization. Concurrently, we will continue to promote the global expansion of clinical research proposals through our system of cooperation with research institutes and university hospitals within Japan and overseas.

**Department of R&D Alliances**

**Search and development of Research proposals**

In order to elicit unused technologies or patents, the Department of R&D Alliances will seek out new technologies and patents by collecting information regarding clinical research proposals from within and outside of the university, and coordinate with researchers about the commercial viability of such technologies.

**Intellectual property management**

To capitalize on research results, provide intellectual property related consultation that extends from before and after patent application with the aim of commercialization.

To improve quality and increase quantity of intellectual property, maximize the value of intellectual property and also plan training for intellectual property management of clinical research.

**Foreign negotiation and Contract**

The department also supports the matching of research proposals that arise from within the university with corporate needs. In addition it also aims to establish a system that can promote technology transfer between domestic and international healthcare companies, and support industrialization and implementation of research resources through licensing activities including clinical evaluation.

**International Cooperation**

In conjunction with the international “science and academic cooperation”, we are involved in international collaboration activities and in international industry-government cooperation activities in life sciences. In addition, we explore the clinical research system and clinical study proposals existing in overseas universities, and thereby support expansion of clinical study proposals through cooperation with overseas university hospitals and research organizations.

**Example of International Cooperation:**

University of Bristol and Cardiff University
Department of Experimental Therapeutics

In order to enable new therapies that are developed through basic research proposals to be applied for clinical use, a wide variety of operations is required from the planning of research proposals to the completion of clinical trials. The Department of Experimental Therapeutics organizes and conducts these comprehensive activities. The activities are composed of the following three areas. First, in response to the consultation from researchers and industry, "Strategy and Planning" promotes support of patent applications with focus on "commercialization" and obtaining fast track regulatory approval. Second, "Project Management" promotes the execution and completion of the project through organizing teams of experts. Furthermore, "Regulatory Negotiation" ensures that the development of drugs and medical devices proceeds efficiently as per regulations. In this way and through these operations we have established a support system that can be implemented smoothly and quickly for investigator-initiated IND/IDE trials.

Examples of achievements of the Department of Experimental Therapeutics:
We have established a support system that can be implemented smoothly and rapidly for investigator-initiated IND/IDE trials.

<table>
<thead>
<tr>
<th>IACT (former Translational Research Center) has achieved the development of several new drugs/medical devices as indicated below:</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of investigator-initiated IND/IDE trials for which clinical trial notification was received</td>
<td>7</td>
</tr>
<tr>
<td>Number of investigator-initiated IND/IDE trials whose clinical study reports were completed</td>
<td>4</td>
</tr>
<tr>
<td>Number of drugs/medical devices that were licensed out to corporations</td>
<td>3</td>
</tr>
<tr>
<td>Number of drugs/medical devices that were approved as advanced medical care</td>
<td>4</td>
</tr>
</tbody>
</table>

Development Strategy

In order to develop research proposals into new practical therapies, it is necessary to build business models with regard to new technologies and drugs, and to plan development strategies for their approval. Furthermore, in order to get medical and regulatory approval quickly, it will be necessary to have effective information sharing and collaboration between industry, academia and government (i.e. companies, researchers and regulatory authorities) from an early phase of clinical development. In addition, such kind of support like patent applications, enterprise negotiations, and fund raising, can also contribute to accelerating clinical development. Through these systems, we aim to contribute to the improvement of health and welfare of people all over the world.

* Tripartite of industry, academia, government agencies.

Project Management

Project Management plays a wide role in the process of development of drugs and medical devices. It deals with resources such as cost, human resources, information, etc. and works on issues related to non-clinical studies, clinical research, and clinical applications. It is thus responsible for ensuring the effective progress of projects.

Regulatory Affairs

When it comes to the development of drugs and medical devices, there is a variety of regulations for processes from basic research to clinical applications. In order to effectively promote such development, the Regulatory Affairs directs communications with PMDA (Pharmaceuticals and Medical Devices Agency), and MHLW (Ministry of Health Labour and Welfare) at the appropriate times and is also responsible for creating consultation documents.
Current efforts of the Department of Data Science include taking advantage of complex information from large scale international collaborative trials and biomarkers that include genomic information to develop new therapies. In response to this move, we have provided the following four divisions. "Biostatistics" to conduct review of clinical trial design, analysis of research data, and to support clinical evaluation from basic research to clinical trial. "Bioinformatics" which supports the development of new therapies with insight into medical needs in cooperation with researchers by using information obtained from genomic biomarker research. "Data management" which ensures accuracy of the data, and deals with the overall operations on data collection for testing the study, and the planning of the study protocol, as well as data handling process such as query, edit check and data corrections. "Monitoring" to verify that the clinical trial was conducted properly in compliance with the regulatory requirements, and that the reported trial data are accurate. The activities of these four sectors makes possible management of a comprehensive set of data from basic research to early clinical trials, manufacturing, marketing and further to post marketing research following marketing approval. Furthermore, based on a database that incorporates epidemiological research, the Department of Data Science provides a research environment for multi-purpose, multi-faceted information analysis.

Bioinformatics is a field that analyzes biological data through the means of information science (informatics).

<table>
<thead>
<tr>
<th>Track record of the past 5 years of support of this division</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statistical analysis, monitoring services and data management</strong></td>
</tr>
<tr>
<td>Investigator-initiated IND/IDE trials</td>
</tr>
<tr>
<td>Advanced Medical B (formerly advanced medical testing)</td>
</tr>
<tr>
<td>investigator-initiated IND/IDE trials. Clinical research</td>
</tr>
</tbody>
</table>

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**Biostatistics**

Biostatistics supports design of clinical trials and analysis of the research data. This is done in cooperation with clinical researchers to develop various kinds of clinical trial designs not just limited to phase I to phase III and based on the clinical objectives. Biostatistics also provides support to appropriately evaluate research data from basic to clinical research. In consultation with medical researchers regarding various issues and problems that arise in their research we will carry out research activities using novel approaches in biostatistics.

**Bioinformatics**

Bioinformatics means the technology used to analyze data from Biology and from informatics by using the vast amounts of data generated by genome analysis and eliciting the gene responsible for a disease. One of the main challenges is to find a cure for the disease by manipulating that particular gene. The operations of the bioinformatics unit is to understand the medical needs by taking full advantage of information obtained in genome biomarker research through close cooperation with researchers and to support development of new treatments. We will continue to simultaneously assess therapeutic prediction bio-markers and their therapeutic efficacy. In addition, we are actively involved in research activities in response to medical queries through a variety of collaborations with the Faculty of Engineering, Faculty of Pharmacy as well as with advanced research institutes overseas.

**Data Management**

Data Management supports overall data collection by carrying out edit check, data query, data correction, as well as participation right at the planning stages of the clinical trial so as to accurately assess the objectives of the trials. In addition, it carries out a whole range of data management functions, such as creation of CRF (Case Report Form), reviews various ways of data entry and decoding data, the design and management of databases, creating data sets for statistical analysis, and thus contributes to consolidation of high quality data. In addition it is also actively involved in the global expansion of clinical trials through introduction of EDC (Electronic Data Capturing) to pursue efficient data management system and is also involved in international joint development projects through CDISC (Clinical Data Interchange Standards Consortium).

**Monitoring**

In order to improve the reliability of the clinical trials, various kinds of monitoring is carried out such as site visits for direct viewing of medical records, central monitoring of collected data, ascertaining that the clinical study is GCP compliant as per protocol and whether accurate reporting is being done. In addition we are considering a monitoring technique that can cope with investigator-initiated IND/IDE trials.

*CDISC (Clinical Data Interchange Standards Consortium) is an NPO that provides standards for international global trial data interchange.*
To practice clinical evidence in Japan and transmit it worldwide through academia-initiated clinical trials, the Evidence Based Medicine (EBM) Collaborative Research Center at Kyoto University was established in February 2001. This institute represents the first collaborative effort for clinical research at national universities in Japan. This center has performed various clinical trials such as the CASE-J study and epidemiology studies over the past 10 years. The EBM Research Department at the EBM Collaborative Research Center aims to create protocols for clinical study, recruit patients, manage data, perform bio-statistical analyses, and promote collaboration amongst physicians. This department also subjects newly approved drugs and medical devices to academia-initiated clinical trials and epidemiological studies.

*EBM stands for Evidence-Based Medicine, which reflects an emphasis upon physicians to use the best research evidence to make informed decisions about the care of individual patients, as opposed to relying simply on empirical observations. EBM also involves taking into consideration patient variability and preferences in making decisions.

**What are post-marketing clinical trials?**

New drugs are generally approved after their safety and efficacy are confirmed in patients through regulatory approval. However, such approval does not include patients with special conditions, such as elderly patients or subjects with liver/kidney dysfunction, and thus the efficacy of a drug in such subjects would be unknown before its usage in practical medicine. As such, we often find out later that there are additional adverse effects or even unexpected efficacies in complicated patients. For instance, between the years 1990-2004, 34 drugs were withdrawn from the market due to safety issues (Clinical Pharmacology 2009). Another example is the ACE inhibitors, which were initially thought to be a miracle drug for renovascular hypertension. However, this drug was later found to be potent enough to reduce blood pressure in patients with essential hypertension. As of today, they have come to be widely used in various diseases such as renal dysfunction and heart failure for their cardio- and reno-protective effect. Given these facts, the safety and efficacy of therapeutic agents are further validated through well designed post-marketing clinical trials of the approved drug. The expansion of indication is thus not necessarily limited to in-vitro studies only.

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**Research Proposal/Plan/Design**

The Department of EBM Research plans the design of clinical studies to validate evidence for clinical questions that arise during clinical practice. Not only does the department implement research plans to address issues derived from academia and companies, but also makes proposals and aims to create even higher quality evidence which will be cited in treatment guidelines.

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**Planning and Negotiations**

The Department of EBM Research also carries out planning and negotiations in order for the clinical studies to be of high feasibility and good quality. Using our wealth of experience, we have made robust achievements in clinical studies by recruiting highly competent physicians with high levels of research activities as well as setting up a research organization of specialists.

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**Clinical Study Promotion**

In order to promote clinical research in Japan, it is necessary to help junior clinical researchers with multiple tasks. Accordingly the Department of EBM Research actively supports junior physicians who have little experience in clinical research. In particular, the department provides junior researchers support in creating the research protocol, coordinating the administrative functions, and helping in data analysis. The department also communicates and negotiates with academia or industry if necessary and are also actively involved in public relations such as seminars and graduate education related to clinical research.
The Department of Clinical Innovative Medicine is responsible for providing operational support to investigator-initiated IND/IDE exploratory trials through organizing a full-time multi-disciplinary team consisting of nurses, pharmacists, clinical laboratory technicians, and physicians. The protocol writing support division reviews the research plan and various types of application forms from a medical and scientific point of view, while promoting the integrity of the documents, and coordinates the multi-disciplinary team so as to produce high-quality research and clinical protocols in a short period of time. The clinical trial management support division bridges the gap between hospitals (clinical departments) and laboratories (investigators/researchers), serving to solve a wide variety of problems that may arise during the preparation and execution of clinical trials. The safety information and compensation division monitors and reviews safety information, and strives to advocate for patients in case of injuries to health. While complying with the latest laws and regulations, the Department of Clinical Innovative Medicine supports the implementation of investigator-initiated clinical trials of unapproved drugs and medical devices from both within and outside of Japan, aiming to obtain regulatory approval and accelerates availability of new drugs and devices. Hereafter we aim to strengthen the “study management” functions especially in multi-center trials, contributing to the creation of new therapies.

### Protocol writing support

The clinical study protocol explains why the trial is necessary and how it is conducted. A precise, step-by-step description of the clinical trial is required for reviews by bioethics committees, Institutional Review Board (IRB), or other administrative and regulatory offices, and is essential for the preparation and execution of the study. The Department of Clinical Innovative Medicine cooperates with not only laboratory investigators and research physicians, but statisticians, data managers and other specialized staff for creating a high-quality, unified study protocol in a short period of time.

### Clinical Trial Management Support

The Department of Clinical Innovative Medicine serves as the “study manager” to prepare for the clinical trial and resolve related problems, collaborating with project managers and other staffs/departments in the Advancement of Clinical and Translational Science (iACT) in addition to physicians and investigators. Our mission is to provide support in advancing each trial efficiently, keeping in mind the provision of better medical treatment and improvement of research standards.

### Safety Information Control/Compensation

The Department of Clinical Innovative Medicine pays attention to the latest laws and regulations and develops procedures for safety information management in accordance with the categories of drug/medical device/biologics, unapproved medical technology and expansion of already approved indications. During the course of the clinical trial, we closely cooperate with physicians, clinical trial coordination offices, and manufacturers who have provided the drugs and medical devices to collect safety information rapidly and accurately, helping principal investigators transmit and submit the information to the local IRB, other institutions if it is a multi-center trial, and other regulatory authorities. We also provide procedures of the indemnification for patients in case of injuries to health.
The Department of Clinical Trial Management, which was officially established within the hospital in 2011, is a cross disciplinary organization that is made up of pharmacy, nursing, inspection, and administration. The Center for Clinical Trial Management had been introduced as its predecessor in 1999. Clinical trials are clinical studies done in human subjects for medical devices and drugs in order to collect data for approval based on the Pharmaceutical Affairs Law. Clinical trials should be consistent with Good Clinical Practice (GCP) which is criteria specified by the authority of the Ministry of Health, Labour and Welfare. In compliance with this standard, we serve as a central trial office as well as the Institutional Review Board (IRB) that maintains the standard operating procedures (SOPs), and perform appropriate document creation and record-keeping. We also act as an interface between the investigators, the trial subjects as well as the sponsors to coordinate the smooth conduct of the clinical trial. In recent years, due to the increasing number of Multi-national and investigator-initiated trials, our activities have become increasingly complicated and sophisticated. We ensure the protection of the rights, safety and well-being of trial subjects, consistent with the principles that were set forth in the Declaration of Helsinki, and through credible clinical trial data. Furthermore, we will take advantage of the know-how obtained from clinical trials to continue contributing to high quality clinical trials that are ICH-GCP compliant to fulfill our mission as a core clinical research hospital.

Clinical trial experience breakdown (2011)
- Achievement: 87 trials (84 industry and 3 investigator-initiated trials)
- Breakdown of industry clinical trials: 76 Medical therapeutics (90.5%), 8 Medical devices (9.5%), 55 Domestic clinical trials (65.5%), 29 Multi-national Trials (34.5%)

Implementation of clinical trial support by the Clinical Research Coordinator CRC
CRC plays the role of a coordinator that stands between the sponsors, trial subjects and investigators to make sure that the clinical trial is carried out smoothly. Since the clinical trials and clinical studies involve research, CRC strives to be GCP compliant, protect the safety of the subjects, support the investigators and coordinate with various departments within the hospital, so as to enable collection of scientific data as per the protocol defined by the sponsors. The CRC aspires to deliver better therapeutics and medical devices for the patients faster, and also provides support for the appropriate execution of the investigator-initiated trials which can then generate evidence to change the medicine of the future.
To effectively develop research proposals amongst universities

Translational research

Translational research helps to make the findings of basic science applicable for clinical purposes through the university’s support of clinical trials and applications. In Kyoto University, through this translational research we hope to generate creative leading pharmaceuticals and medical devices originated in Japan. Translational research also helps find a solution to unmet medical needs and through drug development contribute to creation of economic effects and new industries.

Aim

Strengthening clinical research functions of the university
- The collaborative clinical research efforts of Kyoto University with other universities will propel the clinical research activities of all participating universities
- Sharing of information and interactions between universities regarding clinical research

To contribute to society the fruits of our research
- To conduct multi-center clinical trials so it is possible to obtain more universal results as compared to single-center trials
- To respond sooner to necessary medical needs by finding efficient clinical applications for research proposals held by each university

Status

We are developing a cooperative relationship mainly on universities and university hospitals in central and western Japan.
In the process of this cooperation we will learn what kind of functions are needed and propose new clinical research support.

Support offered

Because the approach and status regarding clinical research differ in each university, Kyoto University will respond individually based on the needs of the respective partners.

Support of clinical research in participating universities
- Acquisition of funds “research proposal class A”
- Acquisition of funds “in-house projects invited from public”
- Acquisition of other research funds

Consultation
- Support related to research proposal evaluations, patenting
- Introducing joint development companies to researchers
- Support regulatory application (advanced medical and clinical trials etc.)
- Writing clinical research protocol
- Biostatistics consultation
- Sharing of SOP, operation manuals and other information and documentation about clinical research

Announcement of clinical research information
- Dissemination of information on a regular basis via e-mail
- Notification of clinical research information
  -Information about research funding and revisions about ethical and GCP guidelines
- Updates about seminars and symposiums
- Enquiries on other matters

Human Resource Development
- OJT [Education for clinical trial professionals [short term]] about one week to one month and [long term] 1-2 years
- Conducting seminars
- Providing educational tools regarding GCP and about clinical research in general
Reference

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