

Recommendations on Clinical Research

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The Purpose of Our Recommendations

Japanese clinical research has been on the decline in recent years, in spite of the policy adopted in the Ethics Guideline for Clinical Studies of 2009 implemented by the Ministry of Health, Labour and Welfare of Japan which states the following: “With the advances in science and technology, clinical research has become increasingly important. Even the methods that have been established as optimal for the prevention, diagnosis, or treatment of diseases need to be continuously reviewed and revalidated in clinical research in order to reconfirm their efficacy, efficiency, convenience, and quality”. Japan’s international ranking in the number of academic papers published has been falling since 2003: Japan is currently in the 18th position. The lack of high-quality clinical research and the lag in data generation or evidence-building from clinical research findings are issues that need to be promptly addressed for the benefit of higher standards in healthcare to our citizens.

There are two types of medical research which intervenes with the clinical care of patients: development trials undertaken by pharmaceutical companies for the purpose of drug licensing approval and those conducted post-approval mostly led by physicians/researchers. In trials conducted by drug companies, there is an inherent limitation of scope of the targeted concomitant therapy or indicated diseases which are dictated by the regulatory requirements. This necessitates post-approval, investigator-led clinical trials for the advancement in medical science and treatment.

The current Japanese situation is such that there are inadequacies in the framework for clinical research. Nor are training opportunities for researchers fully established. Funding for conducting clinical research is not sufficient. What is more, there is an issue of conflicts of interest between pharmaceutical companies, the principal providers of financial support, and research physician groups or medical institutions.

Bearing these things in mind, the Japanese Association of Pharmaceutical Medicine (JAPhMed) set out to identify various issues that need to be tackled in order to further the progress of clinical research and to put forward specific recommendations including actions to be taken. Listed are our recommendations for training and fostering of human resources and organizations, improvement of processes, and concluding of research contracts, together with requests for actions directed to the public, private and academic sectors.

There is currently no consensus among drug companies, research groups and medical institutions on the way clinical research should be conducted in Japan. The recommendations made here have not had assent from all relevant quarters. However, for the thrust required to attain clinical research

of high quality, an essential prerequisite in the advancement of medical care, the JAPhMed believes that urgent steps must be taken and thus has arrived at these recommendations. The JAPhMed also intends to continue to make timely provision of constructive suggestions.

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1. Background

(1) Gap in International Evaluation

In August 2008, the publication of the Office of Pharmaceutical Industry Research (OPIR) of the Japan Pharmaceutical Manufacturers Association (JPMA) called *OPIR News and Views* reported that Japan has now been overtaken by China in the number of clinical research papers published and is now in the 18th position in the world.¹⁾ This was a great shock not only to the pharmaceutical industry but also to the physicians at the forefront of clinical practice. In a report by OPIR's chief researcher T. Takashima which is titled "The status of clinical medical studies and effort towards its improvement: an international comparison using published clinical data," the numbers of research papers published in major journals in both basic medicine and clinical medicine are examined by using tables compiled at five-year intervals. The journals selected are leading publications in each area with a high impact factor: the three journals, *Nature Medicine*, *Cell*, and the *Journal of Experimental Medicine (J Exp Med)* for basic medicine, and the three journals, the *New England Journal of Medicine (New Eng J Med)*, the *Lancet*, and the *Journal of the American Medical Association (JAMA)* for clinical medicine. In basic medicine, Japan had been ranked 6th before 1997 but has risen in ranking since: it has been in the 3rd position after the USA and Germany since 1998. In clinical medicine, Japan had been ranked 12th before 2002 but has fallen in ranking since: it has been in the 18th position since 2003. By contrast to Japan, China is rapidly increasing the number of papers published. Although it was ranked 25th or below pre-1997 in both basic and clinical medicine, it has risen to the 13th position in basic medicine and the 15th position in clinical medicine since 2003. In clinical medicine, China is ahead of Japan. This report also comments on the quality of clinical medicine papers and internationalization. An international comparison of the number of papers and the number of citations per paper in 46 journals of clinical medicine reveals that Japan is 5th in the number of papers but only 19th in the number of citations per paper. This is far below average and is far behind China. Looking at the number of internationally co-authored papers using the United Nations' C-index, Japan comes 24th, indicative of the low level of involvement in international clinical research. A report like this raises concerns about the decline of clinical studies in Japan, and in particular the shrinking number of high-quality clinical research that can provide evidence globally in the context of the age of evidence based medicine. This decline may well lead to delays in access to newly available medical treatment.

(2) Clinical Research Required for Improvement of Healthcare

The Ethics Guidelines for Clinical Studies (EGCS)²⁾ of the Ministry of Health, Labour and Welfare (MHLW) defines clinical research as medical research performed on human subjects with the goal of improving methods of preventing, diagnosing, and treating disease, acquiring a better understanding of the etiology and pathophysiology of individual diseases, and improving the quality

of life of patients. In its Introduction, EGCS states that “Even methods that have been accepted as optimal means of preventing, diagnosing, or treating diseases need to be continuously reviewed and revalidated in clinical research in order to reconfirm their efficacy, efficiency, convenience, and quality” and “Advances in medicine often depend on clinical research,” endorsing the wide-ranging importance of clinical research as playing an essential role in the advance of healthcare.

Thus, expectations are great for clinical research to contribute to the advancement in healthcare; however, as referred to above, clinical research in Japan are actually beset with difficulties. One reason is the “shortage of doctors” occurring in recent years. Clinical physicians, especially hospital doctors are busy with their daily patient care and in effect have no time for clinical research. Meanwhile, physicians today are required to undertake clinical research as clinical specialists and to have the capacity to produce evidence thereby. For example, a requisite for accreditation by the Japanese Society of Internal Medicine as a board-certified member with internal medicine specialty³⁾ is publication of clinical research in a medical journal or its presentation at an academic conference.

(3) Necessity of Investigator-Led Clinical Research

Of clinical research, interventional studies of human subjects are called “clinical trials.” The interventional studies referred here encompass everything other than that is based on the so-called standard treatment which follows package inserts and guidelines. If these clinical trials are categorized by the entity that undertakes research, there are trials undertaken by pharmaceutical companies and trials undertaken by physicians. Clinical trials undertaken by pharmaceutical companies are mainly for the purpose of gaining drug licensing approval (*chiken* in Japanese) and normally are a single-dose study of the drug concerned and the disease treated is strictly specified. However, a patient is often actually treated not with a single drug but with multiple drugs or in concomitant therapy with surgical operation or radiotherapy. Moreover, there may be some related diseases where clinical benefit might be expected pathophysiologically. Such situations of concomitant therapy or indications for related disorders are difficult to accommodate in clinical trials which pharmaceutical companies conduct. This is an area where investigator-led clinical trials are strongly required. Furthermore, when pharmaceutical companies conduct trials, the issue of publication bias arises. Pharmaceutical companies have profit-making concerns and as such are unlikely to publish negative study findings. Publication bias can also occur in investigator-led clinical trials but the rate of publication is assumed to be higher than is the case with pharmaceutical companies. Not only when there are adverse events but when advantage of a new treatment method over the standard method cannot be demonstrated, the physician researcher is likely to think that these findings are worth publishing because such information is important to doctors who are engaged in daily treatment of patients. In 2000, B. Djulbegovic wrote in the *Lancet* that trial results published by companies report in overwhelming numbers that new therapy methods are more

effective than standard methods but results published by governments or NPOs state in slightly larger numbers that the standard methods are more effective than new methods.⁴⁾ To counter such a publication bias, most companies are now disclosing information on clinical trials in their late phase through a public database such as clinicaltrials.gov before the trials begin.⁵⁾ This should resolve the issue considerably. Nevertheless, what this does not resolve are the issues of trial subjects and concomitant therapy because data that can be obtained in clinical trials are limited in scope. Therefore, there is increasing need to promote clinical research based on investigator-led trials.

(4) Technical Stimulation/Promotion of Support Framework

Though the implementation system of clinical trials in Japan has improved in recent years, comments are often made on its lagged development compared to Europe and the U.S. In investigator-led, post-marketing clinical trial, there is no denying that a clear gap exists between Japan and the West. One reason given is that Japan lags behind in technical aspects of conducting clinical trials, including research designing, data management, statistics and monitoring. These technical elements are essential in carrying out research of high-quality and reliability. However, the opportunities are rare for clinicians or researchers to receive training in these technical matters, which means that not many researchers have full understanding. Besides, together with training for researchers itself, a support system on the above-mentioned technical aspects of clinical trials is critical for clinicians or researchers, who are already busy with their everyday clinical practice. Yet, there are currently no human resources to provide systematic support or a properly established system either within institutions such as universities and hospitals or within public-sector entities.

To give technical impetus and promote post-marketing, investigator-led clinical trials, it is important for the public sector or academic organizations to develop clinical research guidelines and make researchers thoroughly understand and to fully ensure their strict adherence. In this regard, the EGCS that went into force in April 2009 holds promise of having impact not only on ethical aspects but also on technical aspects.²⁾ In the frontline of clinical practice, clinical trials (Phase 1–3) should be developed to be comparable in quality to the European and American standards, thereby producing a total impact over improvements in the institutional clinical trial infrastructures and stimulating and promoting the technical aspects of clinical trials in Japan.

(5) Promoting Awareness

The motivation or sense of purpose of clinicians, especially clinical researchers in university hospitals, towards clinical research is low in comparison to basic research. Considering the fact that many clinicians are still obtaining their academic degrees through basic research rather than clinical research, clinicians may well be subconsciously affected by the fact that many universities traditionally emphasize basic research and give relatively low appraisal to clinical research. This

basic research bias in education may have been one of the causes of the lack of awareness about clinical research by clinicians working not only in university hospitals but in general hospitals, and in particular, may have been the root of an impediment to their full appreciation of the ethics aspects. It goes without saying that the subject of the trial must first and foremost be given proper attention in ethical respects. Regrettably, due to this lack of ethics perspective, incidents have occurred in the past where researchers conducted clinical studies without the subjects' consent, thus leading to a public outcry.⁶⁾ It is important to be always respectful of the subjects of clinical studies, be grateful to subjects for their voluntary cooperation, and think of how best to give feedback to the subjects about the research findings. Another issue is the ethical awareness of researchers themselves in financial terms. A recently raised issue is the conflict of interest of researchers receiving donations when developing guidelines for academic societies.⁷⁾ A wide-scale awareness is required not only on the side of individual researchers but also on the side of academic societies or academic journals of how important public disclosure is: even if support for clinical study is to be received from the private sector in the form of a donation, disclosure must be made to manage conflicts of interest.

2. The State of Clinical Studies and Future Challenges

(1) Human Resources and Organizations

Medical education and training in Japan had traditionally been conducted at “departments” of biochemistry, physiology, pharmacology, surgery, internal medicine, pediatrics, and forensic medicine in all the areas of basic medicine, clinical medicine, and social medicine. This was a system which fostered a silo mentally divided by the subject area. In such a context, an interdisciplinary organization concerned with clinical research would rarely be formed. Neither were there instructors who could give specialist training in clinical research. During six years of medical schooling, systematic training for clinical research was virtually nonexistent.

The model core curriculum of Japanese medical schools stipulating the minimum content that all medical and dental students must study before graduation titled “The Model Core Curriculum for Medical Education and Training” produced in 2001 sponsored by the Education Ministry deals with clinical research under ‘F. Medicine/Healthcare and Society (7) Clinical Research and Healthcare’. “Explanation for the purpose of reporting of side effects and adverse events” should be studied before the so-called Common Achievement Tests administered prior to initiating clinical training, and ethics, research designing and other topics should be studied by the time of graduation.⁸⁾ The curriculum thus now includes learning of clinical research during six years in medical school. However, because of historical reasons as mentioned above, there is an absolute shortage of departments and staff that can give specialist training on clinical research.

It has been less than ten years since clinical research support facilities such as clinical research centers began to be created at national university hospitals. Before that, clinicians (physicians who were principal investigators of clinical trials or responsible for the trials) used to carry out the work that clinical research coordinators (CRCs) now undertake, in particular the screening of trial participants, briefing about the trials and obtaining of consent from research subjects. This meant a considerable amount of work for the doctors and also created problems of quality. However, in the past five years the situation has improved across Japan, not only in public or private university hospitals but also in general hospitals. The reasons for this is that the authorities were aggressive to give guidance in addition to the fact that the funds received from the trial sponsor came to be made available to the hospitals concerned and in turn available to the running of the clinical research centers. There are some private universities and private hospitals that consider clinical trials as an important business asset for running their hospitals.

Compared to the clinical trial environment for new drug development, there is virtually no systematic structure that supports post-marketing, investigator-led clinical trials. If physicians are to conduct post-marketing clinical studies, they may receive support in the form of scientific research funds or scholarship donation (unrestricted educational grants) if they are affiliated with university hospitals or hospitals with research facilities. However, it is extremely rare for such funds to be

commissioned to a clinical research center within the institution or to an external support organization such as a CRO (contract research organization).

A vast amount of research funds are required to conduct clinical research of excellence. Public research funds are available from MHLW in the form of the Science Research Fund. In the 2008 financial year, the fund totaled 42.8 billion yen. 1,399 research topics were approved, with an average grant of 20.88 million yen per project. The total amount of grants and the number of grants provided have not changed since 2002 while the newly approved grants has increased from 25% to 30%. However, this is thought to be due to a decrease of roughly 30% in new research applications of 2,399 applications in 2002 to 1,716 in 2008. This situation of roughly 30% decrease in new application over six years cannot be overlooked from the point of view of revitalizing clinical research.⁹⁾¹⁰⁾ Apart from the MHLW Science Research Fund, there are grants from various foundations and academic societies. In many cases, the grant per project is between 500,000 yen to 5 million yen, extremely inadequate sums of money for conducting clinical research. Some universities and large medical institutions have their own project budget or research grant but they are not totally satisfactory in terms of amount or study continuity. Thus the MHLW Science Research Fund and other peer-reviewed research funds are not sufficient in the number approved or the sum granted in the light of undertaking clinical research. The shortfall has to be covered by donations from the private sector. However, the issue of conflict of interest arises, as they can be regarded as inducement to prescription.

(2) Process

A lack of a system for receiving research funds is the primary issue associated with clinical research processes. Many universities and hospitals with research institutions can only receive research funds originating from the private sector in the form of “scholarship donation”, which is comparable to unrestricted educational grants. The word “scholarship” implies that this is a charitable donation (with no requisite on any form of return) made for the benefit of science. This constitutes a framework that is extremely easy for researchers to use. It can be surmised that it makes a certain amount of contribution to the advance of medical research in Japan. Nevertheless, this lacks transparency. There is no obligation to report back to the donor company on the way the money was used so long as it is related to a research topic handled by the department that received the grant. In most cases, there is no submission of any detailed breakdown of expenditure and whether they were used for the relevant research. For research with potential public benefit, the companies may want to provide its financial support through a direct contract, having eliminated issues of conflict of interest and of the promotion code, but universities and hospitals cite a “lack of precedence” as a reason for refusal to enter into a direct contract.

In the case of cancer drugs, post-marketing, investigator-led clinical trials are often proposed to

investigate the effect on cancer types that have not been approved. However, if a company gives financial support to such trials, it may be considered as “promotion of off-label use” from promotion code viewpoint. Therefore, such trials require careful handling and prior consultation with the Fair Trade Commission. To avoid the above-mentioned issues, the company can of course try to obtain such an indication by implementing the trials under GCP (Good Clinical Practice), though in many cases this approach may make no business sense due to the small number of patients for such an indication. Pharmaceutical companies are thus put in a difficult position in determining the best course of action.

Another issue is the capability of the IRB (Institutional Review Board) to review and manage the progress of trials. The IRB needs to have appropriate members to review study protocols from scientific and ethical viewpoints, but the quality of members is admittedly varied, perhaps too varied to review diverse investigator-led trials. Moreover, the review needs to be completed within an appropriate timeframe but due to shortage in resources the review sometimes takes a considerable amount of time. Regarding the management of trial progress, recruitment may falter in research that had already commenced. Then, even in trials that started with a meticulous calculation of the statistically required number of cases, inadequate evaluation of feasibility may lead to the revelation after the start of trials that recruitment of the required cases is utterly impossible with the medical institutions that had been initially planned for. What is more, the direct reporting of safety to the authorities is fairly non-existent.

(3) Strategies and Outcomes

One of the problems with strategies and outcomes is the lack of clarity in the policy on how the research findings are to be used. In short, there are many small-scale clinical research ongoing that seem to be investigating similar research themes without a clear purpose. A recent trend in Japan is participation in global trials as a means of addressing the issue of “drug lag” - the delay in obtaining licensing approval in Japan. The corollary is the diminution of evidence that reflects the distinctive features of Japanese people and the Japanese healthcare environment. Consequently, hope is pinned on post-marketing surveillance and clinical research to build evidence that better matches the Japanese healthcare environment. Indeed, dated February 1, 1999, the so-called “Two Section Chiefs’ Notification” was issued by the Japanese government on the “Handling of Pharmaceutical Drugs in Off-Label Use.” This notification made it possible for doctors to obtain indications of drugs that pharmaceutical companies cannot actively develop. This can be achieved through evidence building from physician-led trials and papers published in international journals. The notification concerns only the drugs that have already been approved and whose use of out of approved indications is requested by academic societies or relevant bodies and is requested by the Research and Development Division of the Health Policy Bureau of the MHLW. The drug use on the

unapproved indications must be described in an internationally recognized standard textbook or in a review article, meta-analysis published in an internationally recognized peer-review journal, or mentioned in a healthcare guideline of an internationally recognized academic society, organization or agency or in a public document published by a regulatory body in Europe or America. However, with the chaotic array of clinical research without proper strategy as described above, implementation of high-quality research and publication of findings remain an issue.

3. Possible Solutions

(1) Altering the Mindset of Healthcare Institutions and Creating/Improving Clinical Research Organizations

The importance of clinical trials is already fairly widely recognized. Major healthcare institutions now have clinical research centers or other facilities that promote these clinical trials. In addition, post-marketing surveillance that is to be administered for the purpose of ensuring the safety of new drugs is being conducted carefully by healthcare institutions with the cooperation of their pharmacy department. It is, however, necessary to become more aware of the importance of post-approval clinical research, whose implementation should be further promoted.

When carrying out clinical research, it is also important to have a clear, identified policy of how the research findings can be used. For example, it can be for inclusion in a package insert to obtain approval for health insurance reimbursement (Two Section Chiefs' Notification) or for assisting in the compilation of a clinical guideline.

Another key point to pursue is the raising of ethical awareness in two areas: the ethical dimension affecting the trial subjects and that involving money transfer. To this end, proper evaluation must be given to clinical research activities, with the result that researchers' motivation improved and their sense of purpose become clearly defined. This will lead to research of high clinical value. The results of the research will produce specific and significant contribution to the subjects of the trials and to the society at large. The measures that can be adopted to solve the problems that exist are as follows. 1. Promoting public relations on the benefits of clinical research and public understanding; 2. Improving Japan's international ranking as a government policy measure in the same way as with licensing approval trials, and 3. Publication and promotion/encouragement of best practice case studies.

In technical terms, support can be stimulated by means of thorough publicity and implementation of EGCS, which should lead to improvement in the mindset of and activities in clinical research. For example, the director of the research-conducting institution must voluntarily make safety reports without fail to the authorities and relevant parties. By sharing information in a timely manner through safety reporting, epidemiological investigation may become possible in collation with the global databases of pharmaceutical companies. The clinical trial promotion centers with CRC in institutions that have been created for drug approval trials can also be used for post-approval clinical research. This would alleviate the burden of researchers and stimulate research.

Because most of the post-approval clinical research is implemented within the approved indication and dosage, in other countries the unit cost of clinical research per patient is deemed lower than that for drug licensing approval trials. Japanese healthcare institutions should calculate appropriately the actual cost incurred for managing post-approval clinical research subjects. For example, a points system (basis for calculating the hospital's expenses in filing its tax return) can be created to work

out the cost per case.

(2) Enhancement of Clinical Research Organizations

For multi-center studies, a legal framework for study organizations is necessary so that multiple participating institutions can conduct joint clinical research. An improved accounting system should also be available to establish financial infrastructure. Already up and running in the public sector are the organizations including the Hokkaido Organization for Translational Research, the National Hospital Organization, and the Foundation for Biomedical Research and Innovation in Kobe; and in the private sector are WJOG, JCOG, JALSG, and JGOG in the cancer domain. The Japan Medical Association Center for Clinical Trials (JMACCT) is intending to widen its scope from merely conducting licensing approval trials to providing clinical research support. Some of these clinical research organizations receive funds from the private sector and sign contracts with several hospitals to conduct clinical research. Future development of such organizations merits attention. To improve the quality of clinical research, IRB and protocol review committees should be enhanced.

Also, the investigators need to agree to a protocol review by pharmaceutical companies in the process of approval for financial assistance towards clinical research. Through global review of study protocols, the drafting and implementation of internationally competitive research can be realized.

Extremely important in the actual management of the research is the role of the department that undertakes the day-to-day operation of trial progress including monitoring and data management. Such departments should have the right and responsibility to check whether clinical research are being conducted properly in each institution. It would thus be necessary to give thorough instruction and to define responsibilities by signing a contract with participating institutions. Monitoring by these departments of whether new cases are being recruited as planned would reduce the waste of money due to unexpected prolongation of research duration. If the relevant managing department can pass realistic judgment on the feasibility of trials, expending precious financial resources on impossible trials can be avoided.

In these respects, the conventional setup of academic societies, research groups and foundations is not currently structured towards conducting clinical research themselves. It is hoped that these organizations will be able to gear up themselves.

(3) Training Doctors and Other Human Resources Involved in Clinical Research

In undergraduate education and training at medical school and in postgraduate training in university hospitals, acquiring clinical research skills must be made mandatory as well as general patient treatment skills. Treating patients, education and research are the missions of doctors who belong to medical university faculties. The principal concern of research for doctors practicing

clinical medicine must be shifted from basic research to clinical research. Doctors should be evaluated more on their contribution to clinical trials and clinical research. Doctors belonging to medical university faculties must refrain from planning observational case studies with no specified purpose, calling them investigator-led research and asking for support from pharmaceutical companies. In addition, clinical research on what is known as a “common disease” is best performed through the work of general practitioners (GPs). Therefore, training on implementation of clinical research is necessary to be provided to GPs.

(4) The Funding Issue

Public research funds for executing clinical research such as the MHLW Science Research Fund should be boosted. In appropriating budgets, allowances should be made for multiple-year, long-term flexibility, as in cases where long-term surveillance is required in making clinical studies of lifestyle-related diseases.

In addition, it is necessary to have a framework where pharmaceutical companies can provide financial support as a matching fund, similar to the program of the New Energy and Industrial Technology Development Organization (NEDO).

(5) Financial Support from Pharmaceutical Companies

Financial support from pharmaceutical companies is to be provided in such forms as donation contract, research grant contract, and research support memorandum. In all these forms, the purpose of research has to be clearly stated in order to prove that no sales promotion is involved and to promote transparency with respect to conflict of interest.

Appendix 1 gives an illustration of what should be confirmed in writing in research grant contracts and research support memoranda. In summary, the followings at least should be included:

1. The research concerned will be conducted in strict adherence to EGCS and other pertinent legislation.
2. The reporting of adverse events must be fully complied with.
3. The research investigator must publish the research, its findings and results on a public database (e.g. JAPIC register)

Appendix 2 gives an illustration of what should be confirmed in writing in donation contracts, in case if support is provided as donation. In summary, the followings at least should be stated:

1. The donation is not a commissioning contract (research results are not to be demanded).
2. Any necessary information must be disclosed.
3. There is no inducement of prescriptions.

With such measures in place to resolve issues, the support towards clinical research will become clearly defined and differentiated, thus gradually reducing the so-called scholarship donation from pharmaceutical companies.

A recent example is the publication of successful research funding bids¹⁰⁾ by the Graduate School of Medicine at the University of Tokyo. In the 2007 financial year, it received 1.5 billion yen in scholarship donation, 2.3 billion yen in contracted research, and, if joint research, COE (center of excellence) and non-COE awards are all included, it received a total of 4.4 billion yen, which is an amount equaling the 5 billion yen received from the MHLW Science Research Fund. The proportion of scholarship donation is decreasing each year. It is probably due not simply to the change in economic climate but due to private companies no longer providing donations without specific and clear purpose of use. Meanwhile, this indicates that with the exclusion of donations, probably all the funding listed might have been specifically allocated in writing to research and other use.

JAMA lists the funds received by US university researchers.¹¹⁾ To build a proper public understanding of clinical research, such information disclosure is also important.

4. Requests for Future Actions

Although the use of new drugs start following regulatory approval of the application of data on their efficacy and safety to the regulatory authorities, there remain areas and facets that have not been fully elaborated before the drug approval is granted. It is, therefore, essential for such data to be investigated through continued clinical research. In Japan, the infrastructure for clinical research is not sufficiently developed. In effect, physicians are conducting post-approval clinical trial on a voluntary basis. The JAPhMed wishes to present the following requests to all parties concerned with the aim that clinical research and trial using approved drugs in Japan attain international standards and that the evidence-based outcomes obtained contribute to the improvement of healthcare and lead to the enhancement of the health of the Japanese people.

Requests to the Government:

The government has adopted measures to promote the improvement of clinical trials conducted for the purpose of obtaining approval for new drugs. We request that similar government support be given to clinical research and trial on licensed drugs as conducted by physicians. In specific terms, we request that a legal framework be expanded and promoted to facilitate clinical research and trial, such as support for the legal incorporation of recognized NPO; that financial support be provided, such as an increase in the Science Research Fund currently available and qualitative improvement of the Rinsho Kenkyu Chukaku Byoin (Clinical Research Core Hospital); and that some regulatory measure be provided so that clinical research and trial results are included in the package inserts in such a way that health insurance reimbursement be applied to them. In clinical trials conducted to obtain licensing approval for new drugs, legislation-based GCP is applied and public regulatory organizations exercise meticulous control; however, for clinical research of licensed drugs, we request that a policy be adopted to ensure adherence to the Helsinki Declaration and EGCS instead.

Requests to the Academic Societies:

We request that academic societies lend support so that clinical research in Japan can stand shoulder to shoulder with the rest of the world as is seen with basic research. Within the range of clinical research activities, clinical trials, in particular, tend to rely on the individual effort of physicians in Japan. As research is often carried out in small or medium-sized medical institutions, a systematic support that networks multiple facilities is required. We hope that academic societies will actively engage in making provision for such support.

Requests to the Industry:

Much of the post-approval clinical research conducted in Japan is funded through scholarship donations or unrestricted educational grants given by private companies. However, clinical research

using such donations or grants from pharmaceutical companies does not always clearly state the details of the research, making it open to accusation of sales promotion and risk of conflict of interest. Transparency should govern the relationships between private companies and physicians or medical institutions. To this end, we propose that a memorandum or contract be drawn when financial support is given to clinical research. Through this means, we hope that world-class evidence established on scientific protocols can be provided to the frontline of healthcare. Furthermore, the signing of a contract will provide a basis for financial planning that goes beyond the current budget year. This would ensure stable business management of medical institutions and clinical research organizations. We also propose that the contract fee be determined by a system similar to the point system applied to drug trials for regulatory approval. The private sector should lead the way in establishing such an economically rational framework. This would lead to the creation of a rational and transparent contractual relationship. Also, the medical institutions can benefit from less administrative burden.

Requests to the Universities:

We propose that the mindset be changed so that clinical research and basic research are given equal weighting and that a curriculum is adopted which properly incorporates clinical research methodology into medical education and training. We propose that exchanges of human resources among the public, private and academic sectors take place so that the right staff is deployed to ensure the above.

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Appendix 1: Details to Be Confirmed in Research Grant Contract or Memorandum Relating to Research Support (Example)

1. Name and address of establishment/physician
2. Name and address of company
3. Introduction
4. Agreement
 - a. To fulfill legal obligation as the trial sponsor
 - b. Corporate responsibilities other than specified responsibilities are to be excluded (e.g. IRB, IC, monitoring, compliance with law and guidelines, trial registration)
5. Responsibilities of the trial sponsor
6. Report on trial progress and communication of data: regular reporting, written report on findings
7. Payment of grant (milestone payment, reimbursement of money not spent)
8. Supply of trial drug
9. Safety surveillance (pharmacovigilance), obligation to report adverse events during designated period
10. Right of company to conduct investigation
11. Response to investigation by regulatory authority
12. Rights over data and publication, review prior to publication of a paper in journal
13. Registration of trial results
14. Effective period of contract
15. Termination of contract
16. Insurance, indemnity, compensation, litigation
17. Confidentiality
18. Conflict of interest
19. Transfer/assignment
20. Contract with third party
21. Change in contractual terms
22. Dispute resolution/procedure
23. Severability of contract
24. Exemption from responsibility
25. Signatures

Appendix 2: Details to Be Confirmed in Donation Contract (Example)

1. Name and address of establishment/physician
2. Name and address of company
3. Purpose
 - a. Research title, sum to be donated
 - b. Reimbursement of donation residue
4. Conditions for donation payment
 - a. After the end of the research, the following should be submitted:
 1. Summary report as evidence that the research was conducted
 2. Report on expenditures
 - b. Payment should comply with fair competition rules and should not be a commission of work (for receipt of results)
 - c. Agreement to disclose/publish to third parties information relating to donation contract
5. Compliance with law and responsibilities of the research organization/researcher
 - a. Who is responsible if damage occurs
 - b. All guidelines/conflict of interest policies must not be violated
 - c. If conflict of interest occurs, this should be reported and appropriate action taken
6. Non-presence of benefit involved in transaction
 - a. Both parties confirm that no benefit is to accrue to them through this donation transaction
7. If a foundation or other delegating body is to serve as intermediary:
 - a. Explanation in writing that a donation cannot be accepted due to accounting rules at the establishment, business plan/previous year's financial report of the foundation, etc.
8. Signatures