LECTURE

Clinical Research in Japan: Past, Present and Future

Yuji Sato and Keisuke Koyama

Centre for Clinical Research, School of Medicine, Keio University
Tokyo, Japan

(Received for publication on September 4, 2009)
(Revised for publication on November 26, 2009)
(Accepted for publication on March 18, 2010)

The volume of clinical research carried out in Japan is relatively small by global standards, especially when compared with the country's contributions to basic research. Although the academic quality of the clinical research done here is generally high, its relative paucity has had a number of alarming consequences, e.g., delays in the approval of important new drugs and medical devices caused by difficulties in clinical trials, leading to the limited availability of novel treatments for Japanese patients. This article aims to present an overview of current clinical research activities in Japan and to summarise the historical, socio-cultural and regulatory issues underlying the current situation. Suggestions are made as to how the present problems might be resolved and how a brighter future for clinical research might be achieved.
(Keio J Med 59 (3) : 104–109, September 2010)

***Keywords*: clinical research, drug lag, clinical trials, research infrastructure**

Introduction

General longevity, comprehensive health insurance coverage and the wide availability of cutting-edge medical equipment, all achieved under tightly controlled healthcare budgets, point to the conclusion that Japan is home to a high level of cost-effective medical science and practice. However, there is a significant disparity between the basic sciences and clinical sciences when it comes to Japanese medical research output as measured by the number of articles published in leading peer-reviewed international journals.[1] This disparity between basic and clinical research reflects the widespread difficulty in Japan of conducting the large-scale clinical trials that form the subject matter of the majority of original articles published in first-class clinical journals. This article attempts first to summarise the present status of clinical research in Japan, second to address the multifaceted issues associated with the country's "clinical research lag", and third to present several paths forward and suggestions for improvement.

Japanese Clinical Research: The Present Situation

Rahman and Fukui[1] have examined via MEDLINE different countries' shares of basic and clinical research articles published between 1991 and 2000 in 13 leading journals, 6 of them basic science journals (*Cell, Nature, Nature Genetics, Nature Medicine, Neuron* and *Science*), and 7 clinical medicine journals (*The American Journal of Medicine, Annals of Internal Medicine, Archives of Internal Medicine, BMJ, The Journal of the American Medical Association, The Lancet* and *The New England Journal of Medicine*). Their results are shown in **Table 1**.

In terms of the share of published articles, Japan ranked 4th in basic science and 14th in clinical research. These results substantiate our contention that there is a significant lag in clinical research as compared with basic research in Japan, although the limited number of scientific journals researched in the study means that some caution is necessary in interpreting the results.

To further examine Japanese research output in relation to the relative productivity of individual research institutions, we carried out a literature search of PubMed. Modern clinical research, in particular that based on

Reprint requests to: Yuji Sato, MD, Centre for Clinical Research, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan, E-mail: yjsato@sc.itc.keio.ac.jp

Table 1 Shares of the 20 top-ranking countries for articles in basic and clinical medicine (from "A decline in the U.S. share of research articles", Rahman M, Fukui T: 2002; N Eng J Med; 347: 1211)

Shares (%) of the 20 Top-Ranking Countries for Basic Science Articles	
Country	1991-2000 (N=23,168)
United States	66.4
United Kingdom	8.4
Germany	4.8
Japan	3.3
France	3.1
Canada	2.7
Switzerland	1.9
Netherlands	1.1
Australia	0.9
Sweden	0.8
Italy	0.8
Israel	0.8
Austria	0.4
Belgium	0.4
Spain	0.3
Finland	0.3
Denmark	0.2
China	0.1
Norway	0.1
New Zealand	0.1

Shares (%) of the 20 Top-Ranking Countries for Clinical Articles	
Country	1991-2000 (N=26,945)
United States	53.7
United Kingdom	18.3
Canada	2.8
Netherlands	1.6
France	1.4
Italy	1.2
Australia	1.1
Germany	0.9
Israel	0.8
Switzerland	0.8
Denmark	0.7
Sweden	0.7
Finland	0.6
Japan	0.6
Spain	0.5
New Zealand	0.5
Ireland	0.4
Belgium	0.3
Norway	0.3
South Africa	0.3

multicentred clinical trials, invariably involves a large number of investigational sites, so we used the affiliation of the first author of each article as the index research organisation representing the publication. **Figure 1** shows the 20 most productive research organisations according to the number of articles (in both basic and clinical medicine) published in English by their researchers and cited in PubMed between 1998 and 2007.

Amongst the top 20 institutions listed, Kyoto University, Tokyo University, Osaka University and Keio University ranked as the 7th, 8th, 9th and 13th most productive, respectively. However, when only the articles published in the 4 leading clinical journals (*The New England Journal of Medicine, The Lancet, The Journal of the American Medical Association* and *BMJ*) are counted, the productivity of these 4 universities drops significantly, as shown in **Figure 2**, whilst the top 5 institutions worldwide (Harvard, Johns Hopkins, Yale, Imperial College London and Stanford) far outrank the others. Notably, Keio University ranks 23rd in clinical research activities in this list (and therefore is not listed in **Figure 2**), and is superseded by other Asian universities.

These analyses suggest first that Japanese medical researchers tend to gravitate towards basic research, and second that only a relatively small percentage of articles by Japanese researchers are published in the four leading clinical journals, which tend to favour articles describing large-scale prospective trials. In other words, there are two sorts of "lag" present in Japanese medical research: first, the lag between basic and clinical research, and second, the lag between articles based on case reports/case series and those based on large-scale trials (the former constitute most of the Japanese clinical articles published in the leading international journals).

Factors Related to the Present "Clinical Research Lag" in Japan

Historical background

In order to import Western science and technology rapidly, it was customary in 19th century Japan to identify the leading Western country in each target specialty as the main source of knowledge. In many branches of the natural sciences, German-speaking countries were designated as the national role models, as exemplified by the

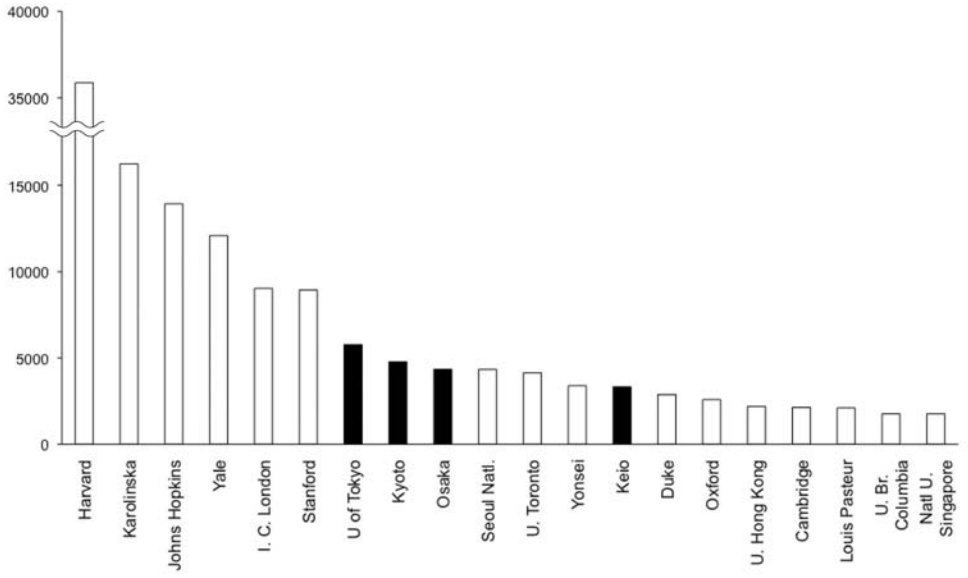

Fig. 1 Number of articles (registered in PubMed, 1998-2007) in both basic and clinical research by the most productive 20 institutions.

appointment of two German physicians as the *de facto* founding professors of internal medicine and surgery at the Western-style medical schools in Japan. This may have helped foster in Japanese medical schools an intellectual milieu where German-style rigorous and systematic basic research was more valued than clinical research. However, von Bältz, one of the aforementioned German physicians, records his observation[2] that Japanese medical students had a propensity to focus more on basic research activities than clinical training, since the former, they believed, would be more advantageous to their career than the latter. It may be reasonable, then, to state that the current Japanese academic orientation towards basic research is a legacy of the intellectual fervour of past generations of Japanese doctors to pursue quick, tangible achievements in their laboratories. One cannot help but be reminded of the resemblance between this 19th-century Japanese phenomenon and the publish-or-perish *Zeitgeist* that would overwhelm academia globally one century later.

The Second World War and its accompanying socio-economic upheavals shifted the hub of science from Western Europe to the United States. Accordingly, Japan switched its primary source of medical knowledge from Germany to the US. However, the basic academic structure in Japan, e.g. the medical education system, underwent few changes. Therefore, at a time when investments to enable large-scale clinical research were being made in the US and elsewhere, no equivalent initiatives were given the priority they deserved in Japan.

The notion of the clinical trial as a valid and reliable method of confirming the effectiveness of novel treatments came into being in the UK in 1948.[3] The first equivalent randomized controlled trial (RCT) in Japan was carried out in 1957. Sunahara argued that the results of these early Japanese RCTs received little international attention, because they involved a number of drugs not approved or used outside Japan.[4] This tendency for Japanese clinical research to be underrepresented overseas, rightly or wrongly, can still be seen today.[5] This may not be because Japanese trials are undervalued elsewhere, but simply because the procedures surrounding the development, evaluation and approval of drugs have differed from those in the rest of the world for such a long time.

In addition to the longstanding Japanese academic predilection for basic research, some industry-sponsored clinical trials of novel drugs have not necessarily met global standards, giving Japanese physicians the impression that clinical research is somewhat less scientifically sound and valuable than basic research. Protectionist governmental policies favouring pharmaceuticals of Japanese origin, along with archaic business practices,[6] may also have helped hold Japanese researchers back from catching up with the flourishing clinical research outside the country.

The advent of ICH-GCP (The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Good Clinical Practice) in Japan in 1997 occasioned belated awareness that Japanese clinical research lags behind in terms of output, quality and infrastructure.

Today, the development of innovative treatments by way of global trials is an efficient way both to minimize the burden of development and to enable quicker regulatory approval of, and therefore access to, novel treat-

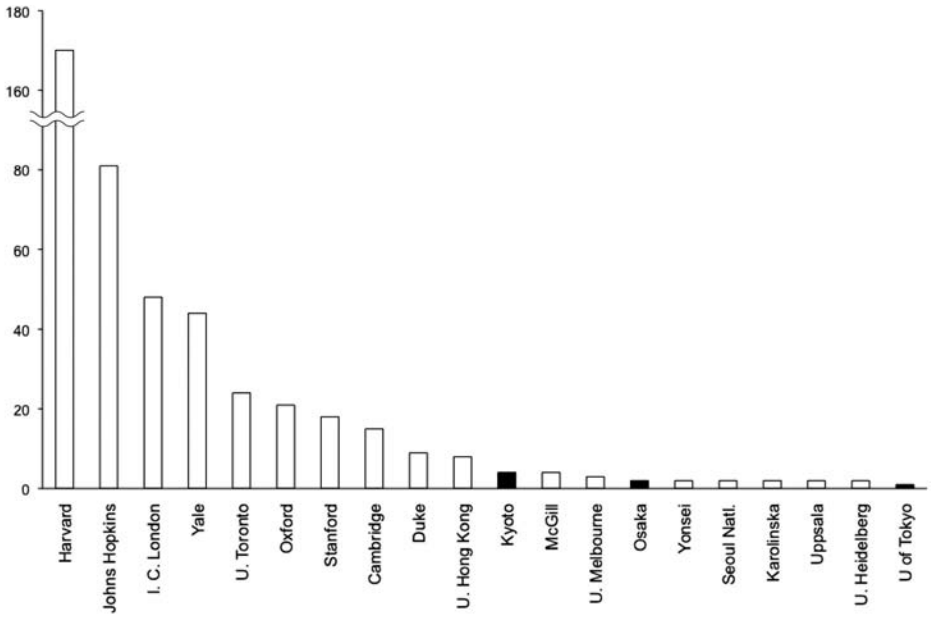

Fig. 2 Number of articles featuring human clinical studies appearing in the four leading clinical journals (N Eng J Med, Lancet, JAMA and BMJ) in the period 1998-2007 by the most productive 20 institutions.

ments. However, the globalization of clinical trials can pose problems[7] despite some countervailing proposals.[8] Although concerted efforts are required in Japan to improve the infrastructure for clinical research, these efforts must be buttressed by high ethical and scientific standards. It is, after all, only natural that the interests of investigators in furthering their careers and the interests of sponsors in seeing trials completed quickly may conflict with ethical considerations and the proper protection of the trial subjects.

Infrastructure for clinical research: hitherto underestimated aspects

It is an outdated stereotype to picture a researcher in basic science as a solitary figure working alone in his laboratory, since in reality almost no basic research is feasible without collaboration amongst many scientists with different subspecialties. Likewise, it is equally wrong to believe that clinical research, in particular long-term, multi-centred clinical trials, can be conducted by a handful of clinicians. As the recently coined term "clinical trialist" (according to the Oxford English Dictionary,[9] its first usage as "One who takes part in clinical tests or trials of new drugs" is attributed to a 1997 article in *The Lancet*[10]) implies, current standards require diverse expertise that can only be provided by a myriad of experts from different specialties. These experts usually include investigators well versed in the disease or therapeutic area in question, research nurses or clinical research coordinators proficient in the operational aspects of trials and related regulations, administrators to deal with the research contracts and financial aspects, biostatisticians and data managers. The availability of these professionals at investigational sites constitutes an important part of the operational infrastructure essential to the smooth, efficient and accurate conduct of clinical trials. This infrastructure is regrettably not in place in Japan, first because the teaching hospitals are generally understaffed, underfinanced and preoccupied with routine health care provision, and second because the aforementioned basic research orientation in Japan means that little attention has been paid to the operational aspects of research. This unfavourable situation has now been recognised, and a number of initiatives for improvement are under way, a prime example being the Ministry of Health, Labour and Welfare's 5-year plan to boost clinical trials.

However, several years before these initiatives were put in place in Japan, the Republic of Korea had already started investing huge amounts of money and energy in establishing clinical research centres, an initiative next to which Japan's efforts pale by comparison.[11] The last several years have seen a dramatic increase in the number of multinational clinical trials carried out in Korea: 148 in 2007, as compared with the 32 conducted in Japan in the same year.

In Japan, against this unfavourable background, various contract research organisations (CROs) have been established in the private sector to assume supplementary roles in research operations. In response to ever-increasing developmental costs and demands to conduct

studies efficiently,[11] the pharmaceutical industry has been outsourcing more developmental functions, e.g. field monitoring and data management, to these CROs.[12] It might seem sensible for academic institutions also to outsource such functions to CROs if all the required functions cannot be set up in-house. However, severely capped healthcare and academic budgets could not possibly cover the costs of outsourcing of this type at the moment, since the pricing structures for these CROs are targeted at industry, making them far beyond the range acceptable to academia.

One critical factor that makes clinical research infrastructure difficult to set up is, as mentioned earlier, the general shortage of medical staff in Japanese academia. According to the OECD's health data 2009,[13] Japan ranks 27th in the number of practicing physicians per 1000 population. Poor differentiation between primary, secondary and tertiary/specialist medical care in Japan has resulted in an atrocious workload for physicians, thereby further restricting their capacity as investigators. The poorly differentiated patient populations at major teaching hospitals can also restrict these institutions' ability to function as effective investigational sites, as they have to accept patients outside the therapeutic areas they specialise in. This negatively affects the number of patients that can be enrolled per site, adding to the already limited enrolment efficiency in Japan.

Last but not least, a fundamental problem affecting clinical research is funding. With the ever-increasing scientific complexity and regulatory requirements associated with clinical research, costs have been rising steadily. One driving factor behind the USA's outstanding clinical research has been the enormous financial support provided largely by the federal government and industry. But this support is now dwindling, which is causing apprehension about the future of academic research in the USA.[14] The problem is all the more serious in Japan, where research funding has always been notoriously paltry.

Socio-cultural factors hindering global trials in Japan

Several socio-cultural factors have served to hinder the creation of an environment in Japan conducive to the conduct of clinical research meeting global standards.

First, protectionist policies applied to the pharmaceutical industry have until recently demanded almost all the required clinical, and even non-clinical, data pertaining to drug approval applications to be of Japanese origin, thereby rendering multinational trials difficult for Japan to participate in. Alleged ethnic differences between the "homogeneous" Japanese population and other ethnic groups, including the Chinese and Koreans, are still often emphasised, even at a time when the concept of ethnicity itself has met trenchant criticism for its politically inflammatory nature[15] as well as for its scientifically untenable premises. This excessive sense of Japanese uniqueness in various areas –pharmacokinetic, socio-cultural, ethnographic, etc.– has almost certainly delayed Japanese participation in global trials.

Second, many Japanese patients seem to be unaware that by taking part in clinical trials they not only make an important contribution to the advancement of medicine but also gain the opportunity to benefit personally from novel treatment. Rather, they are likely to see a request to participate in a trial as coercion into being part of a hazardous experiment. Such negative and ill-informed images probably reflect both insufficient medical literacy and a lack of any sense of altruistic moral civil duty on the part of many Japanese patients.

Future Prospects

Most of the problems discussed above are interwoven with the historical, socio-cultural and regulatory complexities of the country, and are thus not likely to be quickly resolved by implementing a new remedial policy or two.

Nevertheless, improvement of the research infrastructure is a *sine qua non* for the production of clinical research of a high standard, which is in turn essential if the often outstanding basic and clinical innovations produced in Japan are to be recognised and accepted globally, and if novel therapeutic agents are to be quickly approved for use. Furthermore, since emerging Asian countries often have research infrastructures conducive to multinational trials, industry may have even less incentive to sponsor trials in Japan; hence the fear that clinical research in Japan is being "hollowed out". It is extremely important that these problems be tackled urgently and that the existing gaps and lags be filled.

Five practical measures to deal with these issues are suggested:

1) Establishing a proper clinical research infrastructure
2) Providing investigators with higher education in clinical research methodologies
3) Securing sufficient time for investigators to take part in research activities as well as carrying out their clinical duties
4) Improving patients' awareness and understanding of clinical trials to boost their willingness to participate
5) Ensuring transparent and equal collaboration between academia, industry and regulatory agencies

It is to be hoped that these measures will be implemented over the next several years so that the clinical research lag can be rectified. However, given the plethora of far graver issues that the beleaguered Japanese health care system faces, one can only wonder how greater investment in clinical research can be funded.

Conclusion

RCTs are touted as one of the best weapons in the clinical research armamentaria, but they have a number of flaws and limitations.[16] At the very least, RCT results need to be juxtaposed with, and preferably counterbalanced by, those obtained through other forms of research to produce generally acceptable evidence upon which a sound clinical judgment can be made. It is regrettable that RCTs are not infrequently overvalued, regardless of their range of applicability, a situation that has perhaps been brought about by the belated awareness amongst Japanese physicians of RCTs as providers of highly ranked evidence. As a consequence, qualitative, case-based clinical studies have attracted less attention than they deserve. As Rawlins[15] points out, experimentation, observation and mathematics all have crucial roles to play in obtaining clinical evidence. Interventional quantitative research, as epitomised by RCTs, represents only two of these elements, i.e., experimentation and extensively applied biostatistics. Frontline clinical research seems no longer to rely solely on RCTs but attempts to find ways of combining all three elements to obtain a higher level of evidence. If Japan's "clinical research lag" is to be overcome, mastery of RCTs must be accompanied by a widened perspective that encompasses evolving research methodologies. Whether this can be achieved will depend heavily on whether local issues such as the shortage of medical manpower, differentiation between specialist and primary care, healthcare budget restrictions and domestic regulatory complexities are resolved in due time.

References

1. Rahman M, Fukui T: A Decline in the U.S. Share of Research Articles. 2002; N Eng J Med; **347**: 1211.
2. von Bältz E: Das Leben eines deutschen Arztes im erwachsenden Japan, 1931 (Japanese translation, Tokyo, Iwanami, 1979).
3. Pocock SJ: Clinical trials: A practical approach. Chichester: John Wiley, 1984.
4. Sunahara S: Logics and ethics of clinical research. Tokyo, Tokyo University Press, 1974 (in Japanese).
5. Fukushima M: The overdose of drugs in Japan. Nature 1989; **342**: 850–851.
6. Colby MA, Birt MP: Negotiating the Gray Maze – The Business of Medicine in Japan. Connecticut, Floating World, 1998.
7. Glickman SW, McHutchison JG, Peterson ED, Cairns CB, Harrington RA, Califf RM, Schulman KA: Ethical and Scientific Implications of the Globalization of Clinical Research. N Eng J Med 2009; **360**: 816–823.
8. Rozovsky FA, Adams RK: International Research. In: Rozovsky FA, Adams RK: Clinical Trials and Human Research: A Practical Guide to Regulatory Compliance. San Francisco: Jossey Bass, 2003; 535–541.
9. Oxford English Dictionary, 2nd ed. (online), Oxford, Oxford University Press 2009 http://dictionary.oed.com/ (accessed on 17th August 2009).
10. Anonymous: Drug Trials: Allowing for cost. Lancet 1977; **310**: 595.
11. Takahashi K: Drug Development in Japan – Opportunities and Challenges in Drug Development. Int J Pharm Med 2007; **21**: 331–338.
12. Sato Y: Why Japan lags in global clinical studies. BioSpectrum 2008; September issue: 49–50.
13. Organisation for Economic Co-operation and Development: OECD Health Data 2009. www.oecd.org/health/healthdata (accessed on 17th August 2009).
14. Campbell EG: The Future of Research Funding in Academic Medicine. N Eng J Med 2009; **360**: 1482–83.
15. Oguma E: The Myth of the Homogeneous Nation. Tokyo, Shinyo-sha, 1995 (in Japanese).
16. Rawlins M: De testimonio: on the evidence for decisions about the use of therapeutic interventions. Lancet 2008; **372**: 2152–2161.