Table III. Contd

| |
|---|
| non-clinical findings |
| literature sources |
| Late-breaking information |
| Overall safety evaluation |
| discussion on (i) marketed use experience; and (ii) investigational use |
| Summary of important issues (problem list; update of those previously identified and any new ones) |
| identified risks |
| potential risks |
| important missing data (needed to resolve outstanding issues/risks) |
| New actions recommended |
| Conclusions |
| Appendices |

**CCSI** = Company Core Safety Information; **DCSI** = Development Core Safety Information; **MAH** = Marketing Authorization Holder; **SUSAR** = Suspected Unexpected Serious Adverse Reaction.

report than compiling two different but similar reports in parallel, to communicate a single, consistent safety message. The cost of inefficiency and redundancy from having both reports would ultimately fall on consumers and society, and therefore we believe that such duplication should be avoided in line with the ICH's objective of "a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health".[7] Therefore, we believe that the international regulatory community would be better off undertaking the new initiative for integrated periodic safety reporting immediately.

## 3. Main Points to Consider

### 3.1 Preparing for Distribution of DSURs

Several important points regarding the contents of DSURs should be discussed before distribution to ethics committees and investigators. First, concern exists regarding presenting unblinded SUSAR cases in DSURs in terms of statistical validity. We agree with the CIOMS VI recommendation that all SUSAR cases should be unblinded[4,5] and presented in DSURs. In fact, with the aid of adequate allocation methods, disclosing treatment information regarding isolated SUSAR cases would rarely affect the statistical validity of the results from comparative studies. To ensure unbiased comparison of safety results, cumulative incidences of SAEs should be tabulated by treatment arms, including unblinded placebo cases in DSURs.[1,2]

The second point concerns aggregate safety review from clinical trial data. When designing a development plan for an investigational drug, a prospectively planned aggregate safety review within the sponsoring company should be discussed from the perspective of safety risk management.[4] The ICH E2F draft guideline showed the summary tabulation of SAEs across the programme using a simple summation of cases across studies in its appendix.[2] To obtain more useful statistics for early identification of emerging safety risks, we suggest incorporating into the development plan a carefully planned, prospective meta-analysis, which should be performed at a timing to yield sufficient power to effectively detect important safety signals. Drug exposure, doses and characteristics of populations studied should be considered whenever appropriate.[4,8] The results of these meta-analyses should be reported and discussed within the context of overall safety evaluation in a DSUR when available, ultimately aiding in assessing individual case reports and in interpreting results from each clinical trial.[9] Thus, DSURs include the results of periodic assessment of aggregate safety data, and any subsequent changes to the reference safety information should be reflected in the DCSI. Consequent actions taken for risks are determined in the Development Risk Management Plan, ensuring appropriate risk management throughout the development programme (figure 1).

### 3.2 Preparing for Integrated Periodic Safety Reports

Some established practices will be challenged by introducing an integrated DSUR/PSUR model.[1] It may take more years to realize integrated

periodic safety reports, considering the possible difficulties discussed below and the time needed for the DSUR guidelines to reconcile EU Annual Safety Reports and US Investigational New Drug annual reports. The likely barriers to establishing the new processes for integrated safety reports include the need for further harmonization in the relevant local regulations and international guidelines regarding postmarketing safety, and the need to fix the existing chasm in evaluation processes between the departments responsible for development and those for postmarketing safety within the regulatory agencies.[10] Should the regulatory community stop advancing further simplification and improvement of periodic safety reporting processes once the new regulation on separate DSURs is set in place; however, the consequence would predictably be costly, as discussed in section 2.2. Introduction of globally harmonized DSURs will also challenge Japanese regulators and commercial sponsors, in particular, as no annual reports during clinical development phases are currently in place in Japan, and post-approval local periodic safety reports are required to have a harmonized PSUR attached in English. To avoid further burdening sponsors with its unique requirements, Japan's peculiar regulatory system must be harmonized before DSUR implementation.[1]

Postmarketing safety risk management was publicly introduced with the implementation of the 2005 ICH E2E guideline, *Pharmacovigilance Planning*.[11] However, the most recent working PSUR guideline [ICH E2C(R1), 2003] is obsolete in current practice because of its insufficiency in specific instructions regarding contents for risk management.[3] In contrast, the draft DSUR guideline provides detailed instructions for several risk-related sections, particularly as provided under the headings "Overall Safety Evaluation" and "Summary of Important Risks" (table I).[2] When the outdated PSUR guideline is updated, its contents will be expanded to convey important risk information in a globally harmonized manner

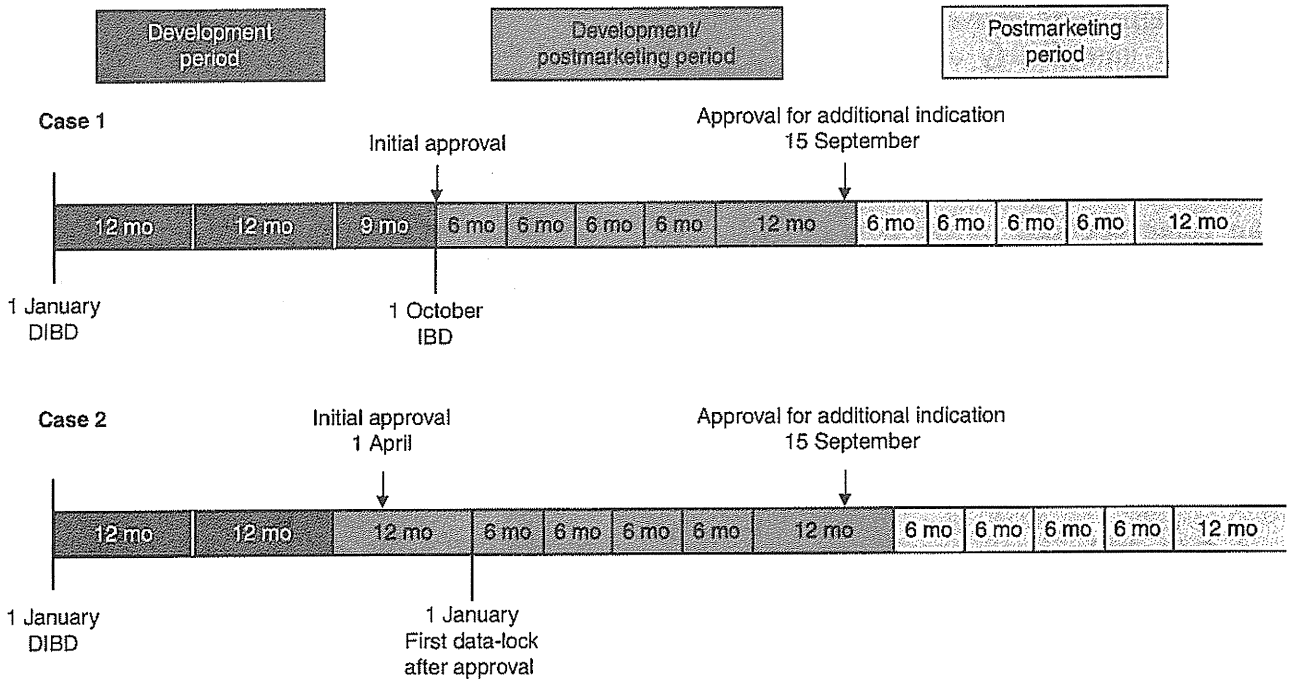


**Fig. 2.** Data-lock points and intervals in a model transition from development phase to postmarketing for a single, life-cycle periodic safety report. Case 1: When the first marketing approval is granted within 6–12 months after the last Drug Safety Update Report (DSUR) data-lock point, the data-lock point for subsequent integrated periodic safety reports after the first approval is changed to the date of first marketing approval, namely the International Birth Date (IBD). Case 2: When the first marketing approval is granted within 6 months after the last DSUR data-lock point, the data-lock point for the subsequent integrated periodic safety reports after the first approval remains as the date of approval of the first clinical trial, namely the DIBD (Development International Birth Date).

at the latest level of regulatory science, as indicated in the model integrated periodic safety reports proposed by the CIOMS VII Working Group (table III).[1] This expectation also supports the concept of a single integrated periodic report.

Synchronization of reporting intervals represents another outstanding issue. We recommend simple alignment of reporting intervals for integrated reports with the current PSUR intervals of 6 months for the 2 years immediately following approval of a new indication, and with those stipulated by the applicable local regulations thereafter (figure 2). Considering the current PSUR intervals and the suggestion for DSURs by the ICH E2F guideline, keeping intervals to less than 12 months would be necessary for the effective periodic evaluation of the flood of postmarketing information immediately after first launch.[2] The model transition from DSUR to PSUR in the CIOMS VII Working Group report permits a maximum interval of 18 months for a DSUR in the peri-approval period,[1] but this duration appears too long for integrated reports to efficiently convey emerging safety information immediately after launch. We also suggest that use of the Development International Birth Date and International Birth Date as a data-lock point for integrated reports should be determined as a matter of convenience, rather than being bounded by the convention of the existing PSUR regulations, to permit a 6-month to 1-year interval in transitioning from a pure DSUR-type report to a DSUR/PSUR-type report (figure 2). Allocation of a sponsor's resources to an approved product during this peri-approval period would typically cover the anticipated workload for frequent reporting.

## 4. Conclusions

The DSUR is a comprehensive and concise document fit for communicating risk information of investigational drugs, including safety-related data and actions for patient protection. Distributing the executive summary of DSURs and ensuring immediate accessibility of full reports to all ethics committees and trial investigators worldwide is strongly encouraged as it may strengthen the clarity of current risk communication and enhance risk mitigation actions by providing a rationale. On taking into consideration both the challenges of introducing an integrated periodic safety report and the anticipated unnecessary burden and confusion likely to arise from simultaneously having two similar kinds of periodic reports for one medicinal agent, we believe that pursuing an approach to a single, life-cycle integrated periodic safety report is worthwhile. Additionally, updating the outdated PSUR guideline to the latest regulatory scientific level following the concept of risk management is introduced is urged.

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SHORT REPORT

# Familiarity and Prudence of the Japanese Public with Research into Induced Pluripotent Stem Cells, and Their Desire for its Proper Regulation

**Ryuma Shineha · Masahiro Kawakami · Koji Kawakami · Motohiko Nagata · Takashi Tada · Kazuto Kato**

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**Abstract** The lack of knowledge of current public attitudes towards basic research into induced pluripotent stem cells (iPSCs) is a serious problem when considering appropriate ways of governance regarding research and its clinical applications. We therefore conducted an internet-based survey to determine public opinion regarding the research and development of iPSCs and regenerative medicine (RM). A total of 14,908 valid responses were collected, which revealed that the Japanese public were familiar with the terms iPSCs and RM, and many of them had received information about iPSCs and RM through the television and newspapers. They also generally accepted the need for extra funding for research into iPSCs, but also decided to adopt a "wait and see" approach and thought that research and development of iPSCs and RM should be conducted under proper governance in accordance with an international regulatory framework. It will be necessary to discuss an internationally consistent regulatory system and effective mechanisms for information flow.

**Keywords** iPS cell · Regenerative medicine · Public attitude · Internet-based survey · Governance

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## Introduction

Science news from Japan and the United States in 2007 regarding the successful generation of induced pluripotent stem cells (iPSCs) through the direct reprogramming of somatic cells in vitro [1, 2] traveled all over the world and impacted upon not only scientific fields, but also the public sphere. In Japan, iPSCs have been reported and discussed in all forms of media. Following a global trend to encourage the research and development of iPSCs and derived products in light of their expected impact, importance and benefits, the Japanese Ministry of Education, Sports, Culture, Science and Technology (MEXT) decided to invest 10 billion yen into promoting the research and development of iPSCs over a 5-year period beginning March 2008 [3].

The importance of adequate governance of advanced science has been discussed previously [4, 5], and this applies to stem cell research. Many factors need to be

**Table 1** List of questions

| Question sentence |
|---|
| 1.Do you know about iPS cells? |
| 2.Do you know about RM? |
| 3.How would you like to find out about iPS cells or RM? |
| 4.How long do you think it will take to realize RM? |
| 5.Which idea regarding research and development into iPS cells and RM is closest to your opinion? |
| 6.What do you think about the cost of research into iPS cells and RM? |
| 7.What do you think about the regulatory framework regarding the medical applications of research and development into iPS cells and RM? |
| 8.Which of the following ideas about the use of iPS cells to make germ cells is closest to your opinion? |
| 9.Do you think that research into iPS cells and RM is necessary? |
| 10.Do you mean 'Is there anyone you know who would like to know more about RM?', or 'Is there anyone you know who would like to receive RM?' |
| 11.Do you have any opportunity to talk about iPS cells or RM in your daily life? |
| 12.Would you be prepared to be actively involved in iPS cell research? |
| 13.What is your attitude towards research into iPS cells or advanced life sciences? |
| 14.How old are you |
| 15.What is your occupation? |
| 16. What is your sex? |

considered in order to ensure proper governance, including social climate and public opinion. Several studies concerning public opinion about stem cell research have been conducted [6–8], but few large-scale investigations have focused on public attitudes towards iPSCs. One exception was a telephone-based survey conducted by a research group at Virginia Commonwealth University (VCU). They asked 1,000 Americans their opinions regarding stem cells, including iPSCs [8]. To the best of our knowledge, no subsequent large-scale investigations into public attitudes towards iPSCs have been conducted, despite the rapid movement forward on governance, funding decisions and iPSC research and development, and the rapid broadcasting of iPSC issues by the mass media. Considering that iPSCs have opened a new dialogue with respect to the basic research and clinical applications of pluripotent stem cells (PSCs), the lack of knowledge on current public attitudes towards iPSCs is a serious problem. We therefore conducted an internet-based survey in conjunction with the Asahi newspaper, one of the most prestigious newspapers in Japan with a circulation of approximately eight million [9]. This survey was open to the public and sought to determine their opinions regarding the research and development of iPSCs and regenerative medicine (RM).

**Table 2** Demographics of respondents

| %(n) | Male | Female | Total |
|---|---|---|---|
| Under 19 | 0.5% (72) | 0.3% (52) | 0.8% (124) |
| 20's | 1.5% (219) | 2.3% (344) | 3.8% (563) |
| 30's | 5.9% (882) | 6.8% (1021) | 12.8% (1903) |
| 40's | 16.3% (2435) | 11.1% (1694) | 27.7% (4129) |
| 50's | 17.6% (2625) | 10.0% (1488) | 27.6% (4113) |
| 60's | 15.1% (2249) | 4.9% (731) | 20.0% (2980) |
| Over 70 | 6.3% (945) | 1.0% (151) | 7.4% (1096) |
| Total | 63.2% (9427) | 36.8% (5481) | 100% (14908) |

## Methods

### Questionnaire

This was a web-based survey. A questionnaire was sent to members of the Asahi newspaper portal site and readers of the Asahi newspaper. Because public attitudes towards iPSCs and RM in Japan are unknown, we designed the questions to determine the public attitude towards and their recognition of iPSCs and RM. This research focused on the public recognition of iPSCs and RM and their opinions concerning the future prospects for and necessary regulation of these techniques, and their willingness to be actively involved. The questionnaire contained 16 questions, including three questions concerning the respondents' backgrounds and a question allowing free

**Table 3** Public familiarity with iPSCs and RM

| % (n) | | Do you know RM? | | Total |
|---|---|---|---|---|
| | | Yes | No | |
| Do you know iPS cell? | Yes | 72.1% (10743) | 1.7% (246) | 73.7% (10989) |
| | No | 15.3% (2275) | 11.0% (1644) | 26.3% (3919) |
| | Total | 87.3% (13018) | 12.7% (1890) | 100% (14908) |

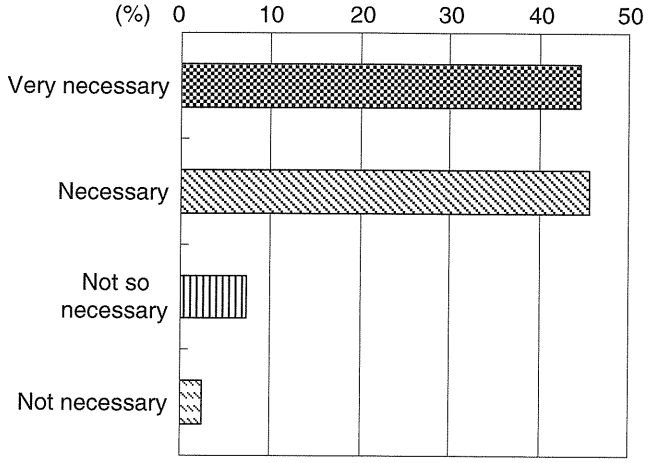



**Fig. 1** Do you think that research into iPS cells and RM is necessary?

description of the respondents' images of iPSCs and advanced life science research (Table 1). The results of this aspect of the questionnaire are not discussed here. We provided a brief introduction to the current situation of iPSCs and RM research, where we aimed to offer information on both the potential benefits and risks of iPSCs and RM, based on the opinions of scientists and the information broadcast in the media. All the questions required the respondents to choose one answer that best described their attitude. A total of 14,908 valid responses were collected in the 5-day period from the 5th to 9 September 2008. We are unable to present all the data here, but report on some of the significant results regarding the current public attitudes to iPSCs and RM in Japan.

To reduce confusion and prevent the questionnaire being too diffuse, we did not ask about people's recognition of research into stem cells or embryonic stem (ES) cells. Although many Japanese people seem to be aware of the terms ES cells and stem cells, it seemed likely that they would not know the difference between different types of stem cells. It was therefore decided that this research would focus on iPSCs and RM, which are the most significant and popular topics with the public in the field of advanced life sciences. A detailed investigation of public attitudes towards other types of stem cell research will follow.

### Potential Biases

The nature of internet-based research is associated with a potential for bias. While it has the advantages of low cost, rapid and easy collection of answers, easy limitation of target respondents, etc., possible disadvantages include a bias towards wealthy and more highly-educated respondents (particularly towards older people who can easily access the internet) [10]. In addition, the respondents were all readers of the Asahi newspaper and internet users, and were therefore possibly more conscious of social problems and had easier internet access than would have been the case had respondents been sampled at random. There were also possible biases in terms of age and sex ratios (Table 2). Respondents under the age of 20 were in a minority, and our results may therefore not adequately reflect the opinions of younger members of the public towards iPSC and RM. However, considering the large number of respondents (14,908), it seems likely that the results of this survey reflect the general Japanese public opinion towards iPSCs and RM.

## Results

### Demographics of Respondents

The demographics of the respondents with regard to age and sex are shown in Table 2. Of the total 14,908 respondents, 63.2% were male and 36.8% were female. Concerning their ages, 0.8% were <19 years, 3.8% were 20–29 years, 12.8% were 30–39 years, 27.7% were 40–49 years, 27.6% were 50–59 years, 20.0% were 60–69 years and 7.4% were over 70 years.

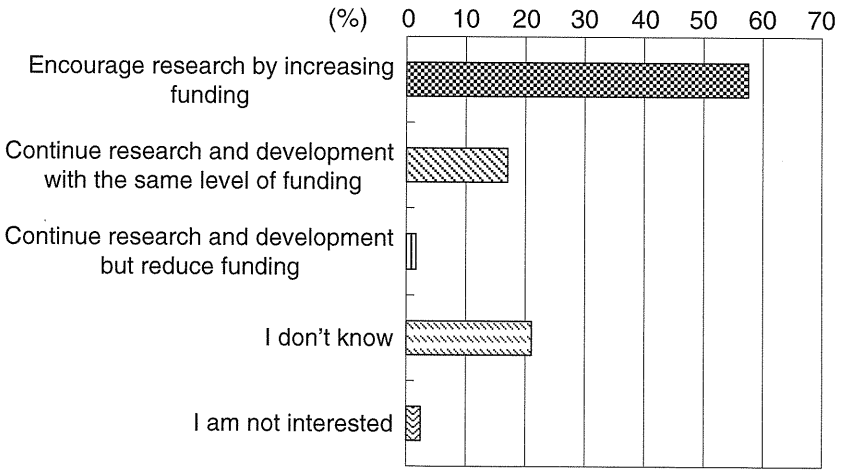



**Fig. 2** What do you think about the cost of research into iPS cells and RM?

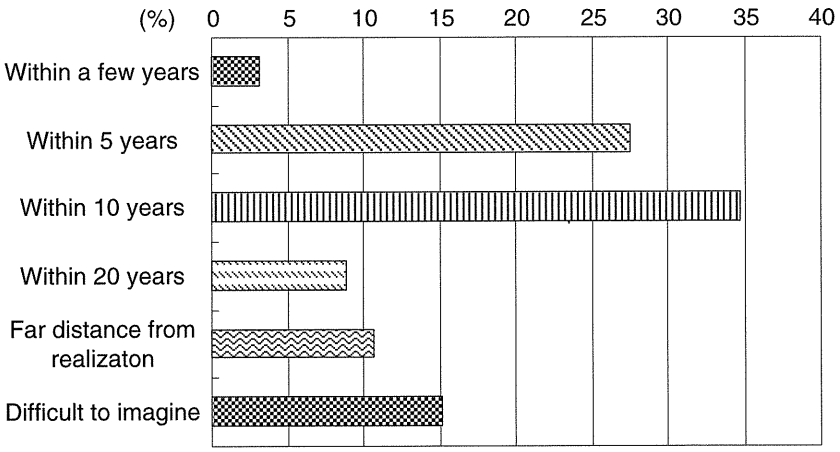



**Fig. 3** How long do you think it will take to realize RM?

## Recognition of iPSCs and RM by the Japanese Public

There was surprisingly high recognition by the public of the terms iPSCs and RM. The term iPSCs was recognized by 73.7% of the respondents, while 87.3% recognized the term RM. The results of a cross analysis of recognition between iPSCs and RM are shown in Table 3. This result indicates that the majority of Japanese readers of the Asahi newspaper were aware of these terms.

## Public Attitudes to iPSCs and RM in Japan

Concerning the necessity for research and development of iPSCs and RM, 44.6% of respondents thought it "very necessary" and 45.7% thought it "necessary" (Fig. 1). In addition, 57.6% believed it should be encouraged with more research funding, while 17.0% believed it should be continued with the same level of funding (Fig. 2). This suggests that many respondents accepted the necessity for continued research and into iPSCs and RM, and the possible need for extra funding. With respect to sex-and age-related responses, there was a tendency for older and male respondents to be more positive supporters of iPSC and RM research (data not shown). A similar tendency was identified when respondents were asked about the prospect of RM becoming a reality; a total of 65.4% said they believed it would be possible "within 10 years" (Fig. 3). Regarding progress and competition in research into iPSCs and RM, 34.9% of the respondents thought that Japan should establish a pioneering research system, and 51.4% of the respondents believed that research and development should progress with international cooperation (Fig. 4).

Concerning respondents' willingness to cooperate with research and development of iPSCs and RM, 21.6% said they would like to cooperate by offering cells and/or blood, but 69.4% said they would like to wait and see the results of further research. Only 9.1% of respondents said they did not wish to cooperate (Fig. 5).

With respect to the collection of information regarding iPSCs and RM, most people said they gained their information from the TV or internet, or from newspapers (73.5%). Contrary to this, 12.4% answered that they would like to search for information using the internet, and 6.0% said they would like to be informed through books or by attending

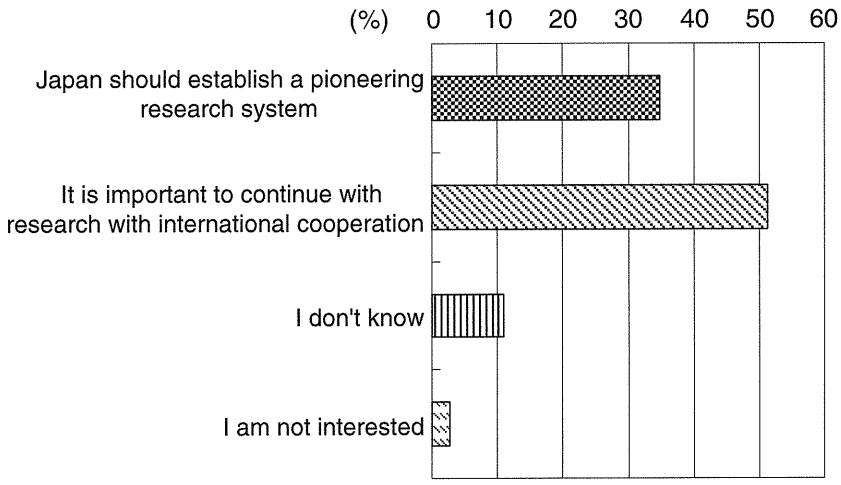



**Fig. 4** Which idea regarding research and development into iPS cells and RM is closest to your opinion?

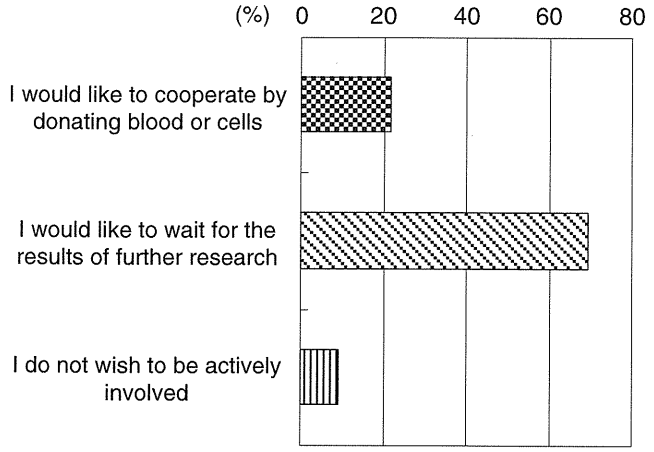



**Fig. 5** Would you be prepared to be actively involved in iPS cell research?

seminars (Fig. 6). 60.0% of respondents had no experiences of conversations about iPSCs or RM.

We also determined opinions about the regulatory framework governing research and development into iPSCs and RM for medical applications. 63.0% of respondents thought that Japan should have a regulatory framework based on international guidelines, while 23.0% thought that Japan should establish a proper regulatory system specifically for the Japanese situation (Fig. 7). The ethical issues surrounding the use of iPSCs to produce germ cells caused 30.3% of participants to respond that they believed the production of germ cells from iPSCs should be banned, while 58.4% thought it should be allowed to progress as long as it was carefully managed and monitored within a regulatory framework (Fig. 8).

## Discussion

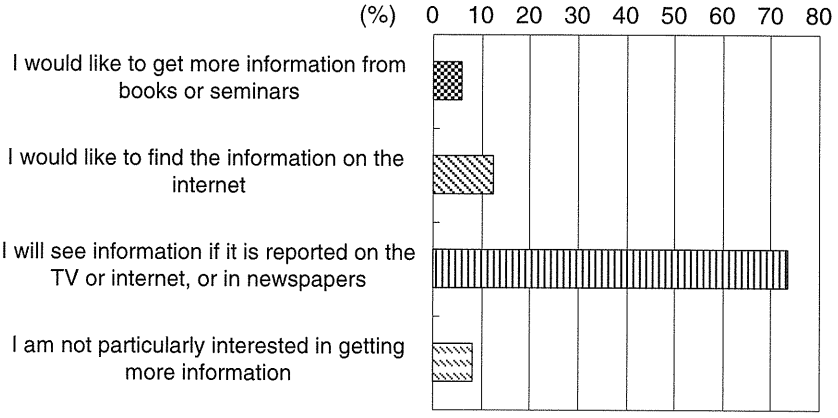
### Public Familiarity with and Prudence Regarding iPSCs

The Japanese public generally accepted the necessity for extra funding and research into iPSCs and RM, and believed that RM would be realized in the near future (Figs. 1, 2 and 3). This high level of recognition of a new type of stem cell was not found in a previous study in the United States [8]. Although the results of these two studies cannot be directly compared, the differences suggest a rapid change in social recognition. Although further studies are necessary, it seems likely that the rapid increase in mass-media broadcasting of iPSCs topics over the past 2 years may be responsible for this increased recognition [11].

It is worth noting that the Japanese public was not motivated to actively cooperate with the research and development of iPSCs and RM by offering their blood or cells at this stage (Fig. 5), but preferred to adopt a "wait and see" approach. Although it is difficult to judge the true meaning of the answers to this survey, the "wait and see" option favored by the public seems to suggest a prudent approach. Interestingly, this implies that a high level of recognition and acceptance of the necessity for research into iPSCs and RM does not directly impact the public's motivation to actively cooperate. In order to investigate this point further, more detailed research into sources of information is needed, given that many people received their information on iPSCs and RM through the media (Fig. 6), and the amount and nature of this information is likely to affect public opinions. A previous study pointed out the possible correlation between public opinion and mass-media broadcasts regarding the issue of genetically modified food in Japan [12]. This aspect will be the subject of future research.

With regard to the sources of information, it should be emphasized that over 70% of the public received most of their information concerning iPSCs and RM solely from the television and newspapers (Fig. 6). Thus the cooperation between researchers, regulatory agencies and journalists is a critical factor when considering the flow of information. Active and effective disclosure of the latest developments in iPSC and RM research, including the risks involved, should be considered, because a balanced information supply is the basis for appropriate governance by the natural and social scientists, policymakers, journalists, and the public. The

**Fig. 6** How would you like to find out about iPS cells or RM?



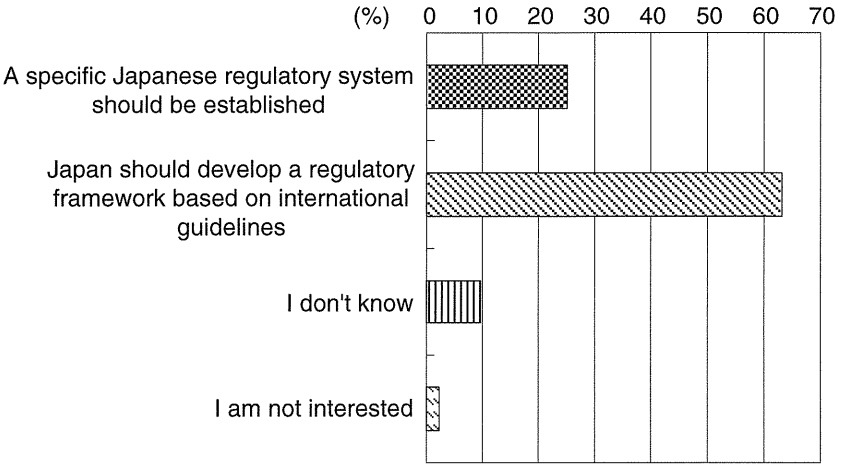



**Fig. 7** What do you think about the regulatory framework regarding the medical applications of research and development into iPS cells and RM?

current situation, with increased interactions between scientists and journalists, works in a positive direction [13].

## Requirement for Governance

It is important to recognize that the Japanese public thought that research and development of iPSCs and RM should be conducted under proper governance, in accordance with an international regulatory framework (Fig. 7). In addition, approximately half of the respondents thought that it was important to progress with research and development with international cooperation (Fig. 4). Thus the establishment of proper governance at the international level needs to be discussed, and discussions relating to the regulatory framework for research and development into PSCs, including iPSCs, are currently being conducted at the highest levels worldwide. For example, several international guidelines concerning general research and the clinical application of PSCs were presented by the International Society for Stem Cell Research (ISSCR) [14, 15]. However, the ISSCR is an academic society and their proposed guidelines cannot be legally enforced in all countries. Moreover, the pace of regulatory developments differs between countries. In January of this year, the United States FDA approved safety evaluations regarding the clinical applications of ES cells [16]. International consensus guidelines are required to cover the safety aspects of such research and its medical applications.

In order to formulate such international guidelines, it is imperative to actively involve regulatory agencies to oversee safety testing, risk evaluation of tumorigenicity and clinical research procedures for cellular therapeutics. Current reports that have discussed the tumorigenicity risk of PSCs have emphasized the importance of appropriate preclinical studies and have pointed out the necessity for rapid discussions on evaluating safety standards and the effectiveness of PSCs in clinical applications [17, 18]. Yamanaka, one of the key researchers into iPSCs and RM, pointed out the risk of cancer due to iPSC implantation in long-term mouse experiments. He emphasized the importance of long-term safety and tumorigenicity risk evaluations [19]. Concerning this problem, a detailed description of regulatory systems will be

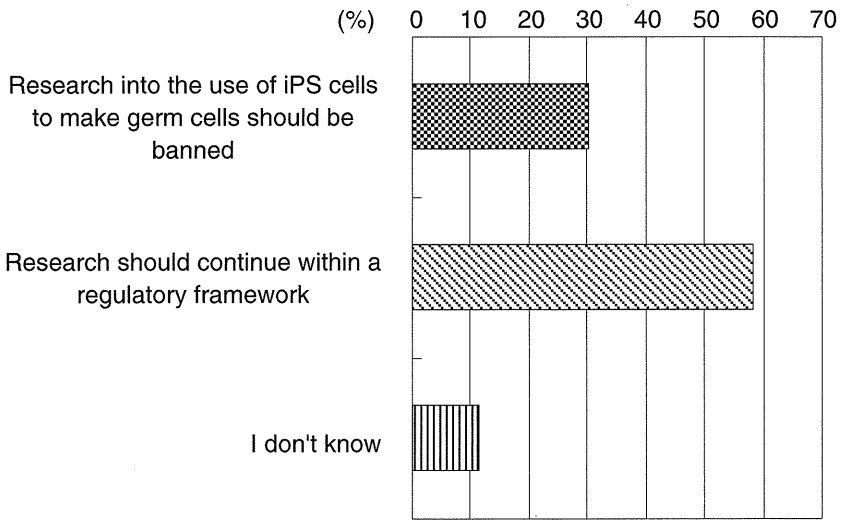



**Fig. 8** Which of the following ideas about the use f iPS cells to make germ cells is closest to your opinion?

needed, considering the potential problems that can arise from imperfect articulation of regulatory guidelines concerning the clinical applications of RM and biologics derived from stem cells [20].

In addition to the safety aspects, ethical aspects are also important. In this study, subjects were asked about the issue of making germ cell from iPSCs. More than half of the respondents thought that research should progress within a carefully established regulatory framework (Fig. 8). In Japan, a MEXT sub-committee approved the production of germ cells from PSCs for basic research in December 2008, though the fertilization of germ cells derived from PSCs is banned [21]. In the present study, we were unable to investigate in detail the public opinion on research concerned with making germ cells from iPSCs. In addition, this investigation was conducted over a different time period from that when the political decision on moderating research into making germ cells from iPSCs was made. Further research into the changes in public opinion and social, political, and scientific changes is needed.

Thus, in order to address the public requirement for the development of proper regulatory frameworks, it will be necessary to establish an international consensus on regulatory frameworks that has domestic legal authority to govern stem cell research and its application in each country. An internationally consistent regulatory system will promote future worldwide research and development into iPSCs and RM

## Conclusion

The results of this study show that the Japanese public was familiar with the terms iPSCs and RM, and that they generally accepted the necessity of research into iPSCs. At the same time, they decided to adopt a "wait and see" approach, and thought that research and development into iPSCs and RM should be conducted under the proper regulations, in accordance with an international regulatory framework. This seems to demonstrate the prudence of the Japanese public. In order to address the public requirements, it will be necessary to discuss an international consensus on regulatory frameworks that have an impact on domestic stem cell research and its application in each country. It is also important to consider the methods of information flow concerning iPSCs and RM, and further research into this issue will be conducted.

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解　説

# FDA「医療機器の臨床試験における Bayes流統計学の利用に関するガイダンス」について

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# On the FDA guidance for the use of Bayesian statistics in medical device clinical trials

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**Abstract**

This article provides the additional information on our Japanese translation, published in the same issue of Rinsho Hyoka (Clinical Evaluation), of the "Guidance for the use of Bayesian statistics in medical device clinical trials", issued in February 2010 by the Food and Drug Administration (FDA), Center for Devices and Radiological Health (CDRH) and Center for Biologics Evaluation and Research (CBER). The guidance referred to four examples of successful use of Bayesian methods in device trials, which were TransScan T-Scan 2000, INTER FIX™ Threaded Fusion Device, BAK/Cervical (BAK/C®) Interbody Fusion System, and InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Devices. We gave explanation of these successful examples in detail, based on the public documents. Although Bayesian statistical methods were used only in the analysis stage of clinical trials in all examples, Bayesian methods are also useful in the design and analysis of clinical trials. In any clinical development of drugs and devices, Bayesian approaches are ideal for earlier phase exploratory trials or proof-of-concept studies as they take into account information that accrues during a trial. Posterior and predictive probabilities are then updated and so become more accurate as the trial progresses. If the relevant external information is available, the decision will be made with a smaller sample size. When using the Bayesian approach in a design of a trial, it is important to have a real collaboration between clinician and statisticians. We hope our translation will contribute to a better understanding and use of Bayesian methods in clinical trials.

**Key words**

FDA (Food and Drug Administration), Bayesian clinical trials, prior distribution, borrowing strength, adaptive design

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## 1. はじめに

2006年5月23日にドラフトが公表されてから4年弱，ようやく2010年2月5日に待望の本ガイダンスが発行された．ドラフトは35頁であったが，本ガイダンスは50頁と分量を含めて大幅な改訂が行われている．説明の追加が大半を占めるが，新たな節として，「4.9 Bayes流の多重性調整」，「4.10 Bayes流の適応型デザイン」，「5.7 感度分析」，「5.8 決定分析」が追加されている．特に，適応型デザイン（adaptive design）については，同時期（2010年2月）に，FDAの医薬品評価研究センター（CDER）と生物製剤評価研究センター（CBER）が公開したガイダンス(案)「Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics, Draft Guidance」を意識してかどうか，Bayes流アプローチと適応型デザインとの相性がよいことが述べられている．

医薬品や生物製品に先がけて，なぜ医療機器にBayes流統計学を導入するかについては，2.2節に述べられている．事前情報が存在する場合については，「良い事前情報は，医療機器の作用機序と進化的開発の理由で，医療機器については利用可能なことがよくある．医療機器の作用機序は通常物理的である．結果として，機器の作用は一般的に全身的ではなく局所的である．その機器に対する変更が軽微なとき，局所作用は前世代のある機器における事前情報から時として予測できる可能性がある．」と医療機器の局所作用が強調されている．しかし一方では，事前情報が存在しない場合にもBayes流アプローチは有用であることが述べられている．また，その節以外において，医療機器特有の問題はほとんど見出すことができない．すなわち，2.2節の記載内容を除けば，本ガイダンスは医薬品や生物製品の臨床試験にほとんどそのまま適用可能であるというのが私たちの印象である．

本ガイダンスには，以下の4つの製品がBayes流の方法を用いて承認に成功した事例として引用されている．事例から学ぶべきことは多いと考え，次章においてこれら事例の解説を試みる．

1) TransScan T-Scan 2000
   資料：http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=p970033
2) INTER FIX™ Threaded Fusion Device
   資料：http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=p970015
3) BAK/Cervical (BAK/C®) Interbody Fusion System
   資料：http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=p980048
4) InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Devices
   資料：http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=P000058

## 2. 成功事例

### 1) TransScan T-Scan 2000

多周波数インピーダンス乳房スキャナーとして1999年に承認されたT-Scan 2000（T-Scan）は，陽性あるいは陰性と判断してよいかどうか疑わしいマンモグラフィー所見を認めた人に対してマンモグラフィーを補助する目的で使用されている．T-Scanの安全性と効果を調べるために以下の3つの臨床試験が実施された．

**①盲検化試験（Blinded Study）**

被験者2,456名のうち，生検された504名（悪性179名，良性325名）の結果から，T-Scanを補助的に用いることによる診断精度（感度と特異度）は，マンモグラフィー単独よりも統計学的に有意に優れており，T-Scanの基本的な臨床的有用性が示された．

**②標的化試験（Targeted Study）**

盲検化試験とは異なり，この試験の目的は

疑わしい病変に標的化したときのT-Scanの診断精度を評価することである．被験者657名により実施され，標的化することによってT-Scanの診断精度は向上した．

③意図された使用試験（Intended Use Study，通称Pistoia試験）

T-Scanを意図された完全な様式（標的化検査および補助的解釈）で臨床使用することが承認された試験センター（Pistoia, Italy）で連続的な生検例74名の試験が実施された．疑わしいマンモグラフィー所見，すなわちLOS（Level of Suspicion）が2または3の場合に，補助的T-Scanの感度はマンモグラフィー単独に比べて統計学的に有意な改善を示したが，特異度に有意な差はなかった（3/6 vs. 5/6, p = 0.50）．

Pistoia試験において疑わしいマンモグラフィー所見が少数（36例）であったため，特異度について統計的に有意な差を得ることができなかった．そこで，以下に示す異なる試験のデータを統合する統計モデルが，意図された使用におけるT-Scanの診断精度を示すために用いられた．盲検化試験，標的化試験，Pistoia試験における疑わしいマンモグラフィー所見データを結合するために，Bayes流多項ロジスティックモデルが用いられた．これは，多項アウトカム，ロジスティック連結関数，Bayes流事前確率および変量効果（Pistoia試験とその他の試験の間で力を借りる（borrowing strength）ため）を取り入れた一般化線形モデルである．

多項アウトカムは，マンモグラフィーのLOS（2, 3）とT-Scan結果（−, +）の4つの取りうる組合せに対応する4つの確率である．生検状況および試験は独立因子としてモデルに入れられた．多項確率のモデル構築に加えて，その確率間のいくつかの差がこのモデルにより計算された．計算にはBUGSソフトウェアが用いられた．真陽性確率における差および偽陽性確率における差に関する結果をTable 1に示す．

疑わしいマンモグラム（LOS 2または3）を有する女性におけるT-Scanの真陽性率（感度）は，マンモグラムのそれよりも約0.156高いと推定され（この差が0よりも大きい確率は98.9%），T-Scanの偽陽性率（1−特異度）は約0.202低いと推定された（この差が0よりも小さい確率は98.0%）．

2) INTER FIX™ Threaded Fusion Device

1999年に承認されたINTER FIX™スレッド化融合機器は，症候性の椎間板変性疾患を有する患者の治療のために使用されている．INTER FIX™機器の前脊髄での使用の安全性と有効性を検討するために多施設ランダム化対照臨床試験が実施された．試験治療患者は腸骨陵由来の自家骨で満たされたINTER FIX™機器で治療され，対照治療患者は同様に腸骨陵由来の自家骨で満たされた大腿リング同種移植で治療された．試験開始後，患者を非ランダム化アーム（INTER FIX™機器でのみ治療されるアーム）に登録することを認めるために試験計画が改訂された．有効性の評価項目は，損傷部位での融合，疼痛／障害状態（Oswestryスコア），神経学的状態，一般健康状態，椎間板高，および総合的成功（overall success）であった．個々の患者に関する総合的成功

**Table 1　Differences in probabilities (T-scan minus mammogram)**

| | 確率における差 | | |
|---|---|---|---|
| アウトカム | 差 | 95% CI | |
| 真陽性率 | 0.156 | 0.024, 0.288 | P (>0) 98.9% |
| 偽陽性率 | -0.202 | -0.388, -0.009 | P (<0) 98.0% |

は，以下の規準に基づいた：融合を示した患者；Oswestryスコアにおける15ポイントの改善；および神経学的スコアの維持あるいは改善（SF-36におけるMCS (mental summary) スコアとPCS (physical summary) スコアにおいて悪化しない）．一般健康状態と椎間板高の結果は総合的成功の計算に含まれなかった．全体の試験は，試験治療と対照治療が術後24カ月時点で同等性を示すようにデザインされた．

181名（77名がランダム化，104名が非ランダム化）が試験治療群，62名（すべてランダム化）が対照群に組み入れられた．Δ（非劣性マージン）0.20を用いると，ランダム化された試験治療群の術後24カ月での総合的成功の割合（37/62, 59.7%）は対照群の割合（17/35, 48.6%）に比べて統計学的に劣っていなかった．

データ解析時点で術後24カ月の評価に達していない約100名の非ランダム化アームの試験治療群患者が存在した．これらの患者が結論に与え得る影響を検討するためにBayes流統計解析を実施した．Bayes流の方法は，次の100名が各臨床パラメータに関して成功するであろう確率を計算できる．Fig. 1にBayes流解析の結果を示す．同等性の予測確率が，臨床的に意味のある最小の値（Δ）の0.00から0.20の範囲において計算された．Δ = 0.04という値を用いたとしても，INTER FIX™機器の結果が対照の結果よりも統計的に劣っていないという確率は0.95を超えている．この結果から，未測定の術後24カ月のデータが結果に影響する可能性は低いと推察される．

### 3) BAK/Cervical (BAK/C®) Interbody Fusion System

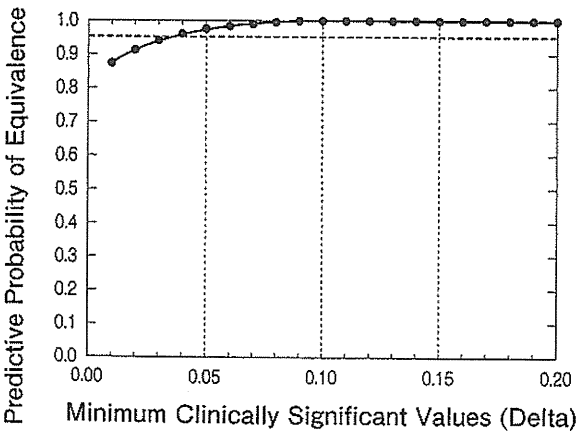
2001年に承認されたBAK/C体内融合システムは，根性症状を伴う頸椎の椎間板変性疾患を有する患者の治療のために使用されている．

BAK/C埋め込みと外科手技（頸椎前方除圧固定術）とを比較した多施設ランダム化対照試験が実施され，機器の安全性と有効性に関する同等性が評価された．有効性の尺度は，患部の椎間板位が融合されたかどうか，頸部疼痛や根性症状（腕／肩疼痛，筋力低下，感覚異常）の緩和があったかどうか，および患者機能（身体的および精神的）における改善があったかどうかである．

298名の患者（試験群164名，対照群134名）が28施設で登録された．患者の追跡検査は術後，治療後3，6，12，24カ月，24カ月以降は毎年行われた．2つの患者コホートが解析のために同定

**Fig. 1 Bayesian predictive probabilities of equivalence***

For overall success - includes second surgery failures




*INTER FIX™ Device No Worse Than Control

Note: Overall success rates were based on patients with available data and did not include deaths, loss-to-follow-ups, or missing observations.

された．1番目の解析コホートは2番目のコホートの部分集団であり，1999年11月までの利用可能なデータからなり，「制限コホート」と呼ばれる．2番目のコホートは2000年6月20日までの利用可能なデータからなり，「非制限コホート」と呼ばれる．制限コホートにおける完全な効果データを有する患者の割合は非制限コホートにおけるそれよりも大きいため，試験の効果に関する結論は制限コホートの結果に基づく．また，制限コホートと非制限コホートから収集された完全な安全性データを有する患者の割合は同程度であり，すべての利用可能な安全性データを含めるために，安全性の結論は非制限コホートの結果に基づく．

BAK/C埋め込みの効果と安全性はBayes流の統計的方法により評価された．ただし，古典的な統計解析が試験結果の解釈を助けるために行われた．Bayes流アプローチは同等性の疑問を直接的に扱うことのできる方法である．効果と安全性の両方に関して，同等性の定義（対数オッズで±0.811の範囲）が事前に設定された．すなわち，対数オッズ比の90%信用区間が完全に+0.811を超えると優越性の結論，完全に-0.811を超えると同等性の結論，-0.811を含むと同等性の強い証拠がないという結論が導かれる．

関心のあるパラメータの事後分布を得るために，拡散事前分布（diffuse prior distribution）が用いられた．事後分布は95%信用区間によって要約することができ，事後分布の95%がこの区間の下限と上限（下限の下に2.5%，上限の上に2.5%）の間に含まれる．頸部疼痛・根性症状の緩和および患者機能の改善を反映する尺度である総合的成功と安全性に関する結果を以下に示す（Table 2～4）．有効性および安全性においてBAK/C治療と対照治療の同等性が示された．

**Table 2　Long-term overall success – Bayesian analysis results (restricted cohort)**

| 尺度 | BAK/C群と対照群の率の差に関する95%信用区間 | 多変量経時的Bayes流解析の結論 |
|---|---|---|
| 総合的成功 | (+9.9, +19.0) | 同等性の規準を満たす |

**Table 3　Long-term overall success – Classical analysis results (restricted cohort)**

| | BAK/C群 成功数／被験者数 | % | 対照群 成功数／被験者数 | % | p |
|---|---|---|---|---|---|
| 6カ月 | 66/114 | 57.9 | 32/83 | 38.6 | 0.009 |
| 12カ月 | 73/124 | 58.9 | 53/93 | 57.0 | 有意でない |
| 長期 | 56/85 | 65.9 | 35/66 | 53.0 | 有意でない |

**Table 4　Freedom from complications – Bayesian analysis results (unrestricted cohort)**

| 尺度 | BAK/C群 (%) | 対照群 (%) | Bayes流解析の結論 |
|---|---|---|---|
| あらゆる合併症なし | 85.1 | 74.7 | 同等性の規準を満たす |
| 追加手術を要する合併症なし | 93.8 | 89.2 | 同等性の規準を満たす |

4) InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Devices

2002年に承認されたInFUSE™骨移植／LT-CAGE™腰部軽減融合機器は，椎間板変性疾患を有する患者の治療のために使用されている．本機器の安全性と有効性を支持する臨床データは，ランダム化アーム（試験群と対照群）と非ランダム化アーム（試験群のみ）からなる多施設試験から収集された．ランダム化アームの対照群は腸骨稜の自家骨で充填されたLT-CAGE™腰部軽減融合機器を埋め込まれ，一方試験群はInFUSE™骨移植／LT-CAGE™腰部軽減融合機器が埋め込まれた．両群での外科的アプローチは開放アプローチであった．非ランダム化アームの被験者は内視鏡下アプローチを通してInFUSE™骨移植／LT-CAGE™腰部軽減融合機器を埋め込まれた．ランダム化アームの対照群は非ランダム化アームの対照としても用いられた．

ランダム化アームには試験群143名と対照群136名が登録され，非ランダム化アームには試験群134名が登録された．追跡率は90%を超えていたが，少数の被験者について，すべての有効性変数に関する完全な24カ月データが利用可能でなかった．欠損値を有する被験者の24カ月データセットを「完全」にするために，存在する12カ月データから24カ月の値がBayes流の統計的方法を用いて予測された．

個々の被験者の成功は主要な臨床およびX線のアウトカムパラメータの各々における成功と定義された．これらのパラメータは以下を含む：

1. X線上の融合の存在
2. ベースラインOswestryスコアからの最低15点の改善
3. 神経学的状況における維持あるいは改善
4. 埋め込み関連あるいは埋め込み／外科手技関連の重篤な有害事象がない
5. 「失敗」と分類される追加の外科的手技がない

個々の主要アウトカムパラメータおよびこれらのパラメータから定義された総合的成功に関する成功確率をTable 5に示す．24カ月の追跡評価データに基づき，成功の事後確率がBayes流の統計的方法を用いて計算された．試験群での総合的成功の確率が対照群の成功確率と同等である確率（事後確率）は，開放アプローチでは99.4%，内視鏡アプローチではほぼ100%であった．

**Table 5 Posterior probabilities of success at 24 months**

| 主要アウトカム変数 | 試験群（開放アプローチ） | 対照群（開放アプローチ） | 試験群（内視鏡アプローチ） |
|---|---|---|---|
| | 事後平均（95% HPD信用区間） | 事後平均（95% HPD信用区間） | 事後平均（95% HPD信用区間） |
| 融合 | 92.8%（88.5%，96.9%） | 88.1%（82.6%，99.3%） | 93.0%（87.9%，97.5%） |
| 疼痛／障害（Oswestry） | 71.0%（63.4%，78.7%） | 70.9%（63.1%，79.1%） | 83.0%（75.6%，90.5%） |
| 神経学的 | 81.0%（74.5%，87.9%） | 81.7%（74.9%，88.7%） | 89.0%（83.1%，94.8%） |
| 総合的成功 | 57.1%（49.2%，65.7%） | 56.7%（48.3%，65.0%） | 68.0%（59.3%，76.5%） |

HPD：highest posterior density（最高事後密度）

以上，4つの事例について公表資料に基づいて解説した．事例1）は他の試験から「力を借りる(borrowing strength)」ためにBayes流モデル（変量効果モデルの拡張）を用いた例であり，事例2）は一部の被験者（非ランダム化アーム）の最終評価時データをそれ以前のデータで予測して主要な結果がどのように変わるかを評価している．これらはいずれも事前に計画された解析ではなく，解析段階で解釈を助けるために行われた解析，いわゆる事後解析と呼ばれるものである．事例3）は計画時に同等性マージンを定義して行われた試験と推察されるが，なぜ多変量経時的Bayes流解析などという複雑な解析が必要であったか，またこの解析方法やモデルは事前に計画されていたか，について資料から確認することができず疑問が残る．事例4）は，事例2）と同様に最終評価時が欠損のデータをそれ以前のデータから予測するためにBayes流解析が行われ，結果が事後確率によって示されている．公表資料から詳細な解析計画を知ることは困難であるが，医薬品や生物製品と異なり，医療機器の臨床試験は探索的な解析と検証的な解析との区別が明確ではないという印象を受けた．

## 3. おわりに — Bayes流臨床試験デザインの開発に向けて

Bayes流アプローチのデータ解析への応用は，物理学をはじめとする多くの自然科学分野および社会科学分野ですでに広く行われている．医学・生物学分野においても，データ解析にBayes流階層モデルなどを適用した事例は数多く存在する．しかしながら，データ解析にではなく，臨床試験のデザイン（実験の計画）とモニタリング（実験の逐次的な監視）にベイズ流アプローチを適用した事例は，悪性腫瘍領域の第I相試験に用いられているCRM (continual reassessment method) を除いては，未だそれほど多くない．

大学等の研究機関で実施するトランスレーショナルリサーチおよび臨床試験には，対象疾患が難治性かつ重篤であり，しかも患者数が限られているという特徴がある．このような状況においては，基礎研究で認められたコンセプトを実証するためのPOC試験（proof of concept study）と呼ばれる探索的な性格の強い試験が主であり，疾患の重篤性などを考えるとプラセボ対照は当然のこと同時対照を設定すること自体が困難な場合が多い．また，被験者のリスクを最小にするために臨床試験の途中で結果をモニタリングしながら意思決定を行うというような柔軟な対応も必要である．さらに，試験の被験者数を最小にするために，存在する証拠や情報（事前情報）を十分に生かすことも重要となる．これらの目的を達成するためには，従来の頻度論的アプローチに基づく推論は試験デザインに完全に依存するため，予期しない事態が発生して試験途中でのデザイン（標本サイズあるいは中間解析の時期や方法など）の変更を行った場合などに，柔軟性などの観点からやや不十分であり，新規臨床試験デザインの開発が不可欠となる．Bayes流アプローチは，柔軟性と効率性の面から有望である[1, 2]．臨床試験におけるBayes流アプローチの主な特長は以下の通りである．

①解釈が容易な「確率」だけを用いて整合性のある推測と意思決定を行うことができる
②標本サイズの大小によらず事前分布を事後分布に更新して推測ができる
③予測分布を用いて試験結果を予測することができる

また，Bayes流臨床試験デザインの動作特性(operating characteristics) が頻度論的に評価可能であることも1つの利点である．

Bayes流臨床試験デザインを用いる際には，臨床研究者と試験統計家の真の協同が重要である．臨床研究者は，既存あるいは外部情報の確かさ，成功確率閾値の見積もり，試験治療の臨床試験を継続するかどうかを決定する確率などについて，専門家としての見解を有している．試験統計家は情報の確かさを含めた事前情報の内容について臨床研究者と議論し，実施可能な標本サイズや被験者の集積率について議論しなければならない．結

果を報告する際には，事後確率が試験開始時から終了時までどのように推移したかを示す必要がある．中止規則の詳細や事後確率の精度（信用区間）のような他の重要な情報も報告すべきである．今後，このようなBayes臨床試験デザインの適用とさらなる開発は，医薬品や医療機器の承認申請にインパクトを与える可能性がある．特に，資源を有効に活用するという観点から効率よく臨床試験を行うことが今後ますます重要になるであろう．

## 文　献

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# Effect of EP4 Agonist (ONO-4819CD) for Patients with Mild to Moderate Ulcerative Colitis Refractory to 5-Aminosalicylates: a Randomized Phase II, Placebo-Controlled Trial

***To the Editor:***

Prostanoids constitute a group of cyclooxygenase (COX)-derived metabolites of arachidonic acid, and include prostaglandin (PG) D2, PGE2, PGF2$\alpha$, PGI2, and thromboxane A2. They are synthesized in response to various physiological and pathophysiological stimuli and function to maintain local homeostasis in the body.[1] PGE2 binds to either 1 of the 4 subtypes of PGE receptor, EP1–4. Among these receptors, EP4 is constitutively expressed in the colonic epithelium and its expression is increased during inflammatory bowel disease (IBD), accompanied by an increase in the amount of PGE2.[2] We previously used knockout (−/−) mice deficient in each EP receptor subtype individually, and found that EP4−/− mice are most susceptible to dextran sulfate sodium (DSS)-induced colitis, and that administration of an EP4 agonist prevents DSS-induced colitis in the mouse through both regeneration of the intestinal epithelium and suppression of the immune response.[3] Based on these findings, we proposed that an EP4 agonist could be used for the treatment of patients with IBD. In that there is no previous clinical trial examining the effects of EP4 agonists on patients with ulcerative colitis (UC), we designed a clinical trial to assess the efficacy of intravenous administration of an EP4 agonist, ONO-4819CD, on disease activity and peripheral cytokine phenotype in patients with mild to moderate UC.

This study was a phase II, randomized, double-blind, placebo-controlled, multicenter trial that recruited patients from 3 centers (Kyoto University, Shiga University of Medical Science, and Osaka City University) in Japan. We defined eligible patients as those who were over the age of 20 years who were diagnosed as active UC by flexible endoscopic examination despite treatment with more than 4.5 g of salazosulfapyridine or more than 2.25 g of mesalazine for 2 or more consecutive weeks, and had symptoms of mild to moderate activity as determined by a Disease Activity Index (DAI) score of 3–9 at study entry as described by Sutherland et al.[4] Exclusion criteria included Crohn's disease (CD), infectious or ischemic colitis. Patients were also excluded if they had severe UC requiring operation or fulminating disease, or had a history of malignancy, uncontrolled diabetes mellitus, or significant cardiac, pulmonary, hepatic, or renal diseases. The use of corticosteroids was not allowed within 2 weeks before enrollment and immunosuppressive medication for UC such as azathioprine, 6-mercaptopurine, methotrexate, tacrolimus, and cyclosporine were not allowed within 3 months before study entry. The study was approved by the institutional ethics committees at each site before patient enrollment and conducted according to the Good Clinical Practice Guidelines and the principles of the Declaration of Helsinki.

We randomly assigned patients into either placebo or active drug group (ONO-4819CD) at a ratio of 1:1 by use of stratified block randomization. Patients assigned to active drug group received 2-week consecutive infusion of ONO-4819CD at a dose of 36 ng/kg body weight dissolved in physiological saline twice a day in combination with mesalamine or sulfasalazine, while those assigned to the placebo control group received infusion of the same volume of physiological saline alone.

Eligible patients underwent a complete history taking and physical examination at the baseline study visit. The extent of UC was determined by colonoscopy. A flexible colonoscopy was performed at the baseline visit to confirm the presence of active disease. DAI score was calculated to confirm the presence of mild to moderate disease activity. Biopsy samples collected from the area representative of disease activity between 5 and 15 cm from the anal verge and histological findings were assessed by a central reference pathologist according to Matt's classification (1 = Matt's grade 1 through 5 = Matt's grade 5). We further performed intracellular cytokine assays for IL-10, IL-4, and IFN-$\gamma$ on peripheral CD4 T cells before and after ONO-4819CD therapy by flow cytometry. The assessments were done at baseline and 2 weeks after treatment.

The primary endpoint was clinical remission defined by a decrease in total DAI score of more than 3 points at 2 weeks after treatment. Secondary endpoints were changes in histological scoring according to Matt's grade, and peripheral cytokine phenotype of CD4 T cells. Safety was evaluated by adverse events and changes in plasma biochemistry and hematologic values.

Planned sample size was 20 patients per arm, which will have 80% power to detect 50% improvement of response probability in ONO-4819CD group assuming response probability of 10% in the placebo group. All statistical analyses were performed using SAS v. 9.1 (SAS Institute, Cary, NC).

Seven eligible patients were enrolled between February 2006 and March 2008 from 3 institutions. Although the planned sample size was 20 patients per arm, enrollment was finished at 7 patients. Four patients (4 male; mean age 39.7 ± 13.5; mean DAI 7.0 ± 2.0) received ONO-4819 CD and 3 (1 male, 2 female; mean age 54.4 ± 8.0; mean DAI 6.3 ± 1.5) had placebo. Four patients were afflicted with left-


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