

The Plan for Promotion of Medical Research and Development

Approved by the Headquarters for Healthcare Policy

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Introduction

<New Horizons in Medical Research>

Recent advances in science and technology, such as in the life sciences and information and communications technology, have resulted in exponential development of innovative medical technology worldwide. In Japan too, innovation in the field of medical care is anticipated. In particular, in the field of medical research aimed at conquering disease and building a healthy society, the goal of research is to develop medical technology that will be used in clinical settings. However, there are many issues that must be overcome in order to achieve this.

To make concrete use of the results of basic science in overcoming disease, we must above all be aware of the importance of wide-ranging basic research based on innovative thinking by researchers, and build the infrastructure for this. Accordingly, the government will continue to promote these efforts. In particular, it is necessary to promote basic research concerning diseases; that is to say, research that sheds light on the pathophysiology of diseases and identifies the mechanisms of the maintenance and failure of homeostasis. The concepts developed through such basic research will be used to examine diseases in humans and will lay the foundations for the development of drugs and medical devices for use in treatment and diagnosis. However, to enable new drugs and medical devices to be used in clinical settings once their safety has been confirmed, clinical research¹ and trials must be carried out in accordance with regulations and guidelines. Furthermore, even after medical technology has been introduced in clinical settings, its effectiveness and, in particular, its effects on prognosis must be verified against those of other technologies by means of clinical epidemiological research covering numerous cases. In the process of verification, it is necessary to identify new issues arising in clinical settings and to feed these back to basic research. Thus, a cycle that encompasses both basic research and clinical settings (cyclical research and development: a type of PDCA cycle) must be established in medical R&D. What is important is to ensure that collaboration with society – particularly compliance with research ethics and efforts to ensure transparency – is a requirement in medical R&D focused on humans. Consequently, research must have clearly-indicated objectives and goals, and be conducted via a system that is fit for purpose. Furthermore, not only research funds, but also the cultivation of diverse

¹ This refers to medical research focused on humans that is carried out for the purpose of improving disease treatment strategies in medical care, understanding the causes of disease, and improving the quality of medical care for patients; it excludes trials as defined in Article 2 (16) of the Pharmaceutical Affairs Act.

personnel, the development of information systems, data management, and other infrastructure, and collaboration with the regulatory authorities are essential in order to link R&D to innovation. Accordingly, it is vital to establish a social system that will enable this to be achieved.

Research that involves deploying the results of basic life science research in the development of medical technology has come to be called translational research (TR) in recent years. The translation of research involves a number of important steps. These include, for example, 1) considering therapies by using life science technology and knowledge to analyze pathology in biological specimens such as disease cells and animal models; 2) considering whether the pathology or therapeutic effect in laboratory animals can be applied to human pathology; and 3) developing new diagnostic and therapeutic techniques and deploying them in clinical research. In TR, it is vital to ensure regulatory compliance in terms of ethical, legal and social implications (ELSI) in the handling of life and limb resulting from advances in research, as well as in conducting clinical research and trials. From the perspective of promoting medical innovation, there are high hopes concerning such research in the field of clinical medicine. This is a new multidisciplinary academic activity involving collaboration between society and scientists, so it is a particularly important issue in Japan's science and technology policy.

The research on which this Plan focuses is also closely related to research based on collaboration between industry, academia and government. Universities have not always had systems that adequately facilitated academic-industrial collaboration, so the development of such systems in Japan has been progressing rapidly in recent years. In moving such efforts forward in future, it will be necessary to take into account the need for practical applications with a direct link to business creation and innovation. Consequently, this Plan is also important in terms of promoting highly-transparent research in Japan, based on collaboration between industry, academia and government in the fields of basic medical science and clinical medicine. In formulating R&D policies and selecting projects, the government will respect judgments based on scientific rationality and transparency, giving due consideration to detailed studies by experts concerning medical needs and feasibility.

<Perception of the current situation in the field of medicine and the launch of new medical R&D initiatives>

Japan has already become an ultra-aging society ahead of the rest of the world².

² The average life expectancy in Japan in 2010 was 79.55 for men and 86.30 for women. The

Changes in the demographic structure are already affecting Japan's society and economy in various ways, with even greater impacts anticipated in a broader range of fields in future. In light of this social background and the approach to medical research described above, the translation of Japan's basic scientific research into efforts to promote the development of the world's most advanced medical technology and the extension of healthy life expectancy through medical care that utilizes the results of these efforts is a pressing issue, as is the need to ensure the sustainability of Japan's health care system. Moreover, it would be fair to say that medical care initiatives focused on the children who will support our society in the future are currently inadequate.

In conjunction with this, cultivating industries in the field of healthcare and medical care as strategic industries and promoting them worldwide as a model for overcoming an ultra-aging society through their contribution to economic growth³ has become a key policy issue.

Consideration of new medical R&D initiatives grew out of the awareness of these issues and specific responses have begun to be implemented.

<Deliberations and progress to date>

On June 14, 2013, the Japan Revitalization Strategy was formulated as a new growth strategy for our nation, aimed at breaking free from more than two decades of stagnation and revitalizing the Japanese economy. This Strategy sought to create new markets by using the issues faced by Japan as a source of inspiration, positioning the extension of the nation's healthy life expectancy as one of the key pillars in the Strategic Market Creation Plan. It described the goal of initiatives focused on this theme as being the realization of the following specific three-point vision for the society that Japan should have by 2030.

- A society where people are able to live a healthy life and get old, by enhancing health

proportion of the total population accounted for by elderly people aged 65 or above is expected to continue to rise from the level of 23.3% recorded in 2011, reaching 39.9% in 2060. At the same time, the number of elderly people aged 75 or over receiving treatment for chronic conditions and their disease morbidity rate is rising due to the escalating aging of the population, as is the number of those requiring nursing care. Accordingly, the gap between average life expectancy and healthy life expectancy must be reduced. (Source: Ministry of Health, Labour and Welfare, The 21st Life Tables; Annual Report on the Aging Society FY2012)

³ The global market for medical care underwent sustained growth at an average rate of 8.7% annually between 2001 and 2010, and was worth around ¥520 trillion in 2010. Japan's trade deficit in drugs and medical devices is growing, reaching about ¥2 trillion in 2011. (Source: Calculated by the Cabinet Secretariat based on data from the WHO, etc.)

management and effective preventive care services

- A society which can provide the necessary medical care at the world's most advanced level by activating medical-related industries
- A society where people unable to work due to illness or injury can return to work as quickly as possible by receiving better medical and nursing care

In other words, as well as the perspective of innovation, it aims to achieve a society in which an appropriate environment has been established, in which citizens themselves not only strive to prevent disease and maintain their own health, but also can purchase ultra-early diagnosis and other appropriate preventive care services from among a diverse range of options and, where necessary, receive the world's most advanced medical care and rehabilitation services.

Medical R&D has been showcased as one of the initiatives aimed at achieving such a society, with the government deciding to create a system that will serve as a control tower, in order to build a mechanism for ensuring integrated support and management of medical R&D, the smooth translation of basic research into clinical research and trials, and the implementation of high-quality clinical research and trials.

In conjunction with this, the Healthcare Policy (hereinafter “the previous Healthcare Policy”) was compiled as an agreement between relevant Cabinet ministers on the same day as the Japan Revitalization Strategy. The previous Healthcare Policy set out the overall direction of efforts focused on creating new services (creating an industry focused on extending healthy life expectancy), developing the infrastructure for new technologies and services, and international expansion of medical technology and services, as well as creating new technologies (R&D and practical application).

On August 2, 2013, the Cabinet approved the establishment of the Headquarters for Healthcare Policy (Director-General: the Prime Minister) within the Cabinet, to be the headquarters for efforts to promote the growth strategy relating to healthcare and medical care, and for control tower functions focused on medical R&D. On August 8, the Headquarters decided to establish the Expert Panel on Medical R&D to study and consider from an academic and technical perspective specialist matters relating to the formulation of a comprehensive policy concerning medical R&D. This expert panel conducted deliberations and compiled the Comprehensive Policy on Medical R&D (Report) (hereinafter “the Expert Panel's report”) on January 22, 2014.

On May 23, 2014, the Act on Promotion of Healthcare Policy (Act No. 48 of 2014), which provided the legal basis for the establishment of the Headquarters for Healthcare Policy, among other matters, entered into force, along with the Act on the Independent

Administrative Agency of Japan Agency for Medical Research and Developmentt (Act No. 49 of 2014), which established an incorporated administrative agency to carry out duties relating to medical R&D and efforts to improve the environment for this.

<Positioning of the Plan for Promotion of Medical Research and Development>

The Plan for Promotion of Medical Research and Development (hereinafter “this Plan”) prescribed herein has been formulated by the Headquarters for Healthcare Policy (Director-General: the Prime Minister), in accordance with the Healthcare Policy (approved by the Cabinet on July 22, 2014), based on Article 18 of the Act on Promotion of Healthcare Policy. The purpose of this Plan is to intensively and systematically promote the measures that the government should implement concerning medical R&D, the improvement of the environment for this, and the widespread adoption of the outcomes thereof. Moreover, it has been prepared to enable the Japan Agency for Medical Research and Development⁴ (hereinafter “AMED”) to play a core role in providing support for both medical R&D conducted using the capabilities of research institutes and medical R&D conducted at research institutes, along with efforts to improve the environment for both kinds of R&D, in accordance with Article 19 of this Act.

This Plan covers the period of five years from FY2014, foreseeing the next ten years. In accordance with this Act, it prescribes the basic policy on medical R&D, intensive and systematic medical R&D measures and the specific targets and time frames for their achievement, and the requirements for the intensive and systematic promotion of medical R&D measures, taking into account the Expert Panel’s report.

Rather than simply copying other countries, this Plan seeks to establish an understanding of the current situation and direction of moves in various other countries, and to capitalize on Japan’s strengths in promoting unique initiatives for overcoming the issues that our nation faces, utilizing our existing human resources, facilities, equipment, and systems to the fullest extent, while taking any additional measures required.

I. Basic Policy on Medical R&D

1. The Specific Vision for the Future that the Plan for Promotion of Medical Research

⁴ Pursuant to the provisions of the Act for Establishment of Laws and Regulations Related to the Enforcement of the Act to Partially Revise the Act on General Rules for Independent Administrative Agency (Act No. 67 of 2014), the Japan Agency for Medical Research and Development will change from an incorporated administrative agency to a national research and development corporation on April 1, 2015, with this change being reflected in AMED’s Japanese name.

and Development is Expected to Achieve

The specific vision for the future that this Plan is expected to achieve is described below.

(1) A country capable of providing world-leading medical care to its citizens

(a) Extending the “healthy life expectancy” of the nation

In 2010, the gap between average life expectancy and healthy life expectancy (the period during which people can engage in daily life without any constraints) for Japanese citizens was 9.13 years for men and 12.68 years for women. Reducing this gap by extending healthy life expectancy in future can be expected to not only prevent a decline in quality of life for individuals, but also alleviate the social security burden⁵.

Health and disease are not necessarily discrete states, so rather than providing treatment-focused medical care alone, it would be preferable to be able to offer disease projections with a high level of probability and early diagnosis before patients actually become unwell, and to attach greater importance to initiatives that employ appropriate measures to prevent the onset, complication, and exacerbation of conditions.

Moreover, it is anticipated that personalized medical care, which combines health and medical information with genomic information, will become a reality, as research into the relationship between genetic information – including the epigenome – and disease is progressing rapidly, due to remarkable progress in genetic analysis technology in recent years.

(b) Achieving medical care that meets the expectations of the people and society

Medical care that can meet the needs of patients and society more accurately is another extremely important vision for the future that medical R&D is expected to translate into reality. Accordingly, in addition to preemptive medicine, such as measures undertaken before onset, there is a need to strengthen evidence-based medical care as far as possible, and to implement appropriate initiatives focused on needs that are currently not being served or are not adequately served with the drugs and medical devices available today.

More specifically, the government will undertake initiatives aimed at gaining a precise understanding of the needs of patients – including from the perspective of quality of life after treatment – and of citizens and society as a whole in relation to a

⁵Source: Expert Panel on the Plan for the Next National Health Promotion Campaign, Regional Subcommittee on Health Preservation, Health Promotion and Nutrition, Health Science Council: Reference Materials for the Promotion of the Second Health Japan 21 Project

diverse range of conditions. These include cancer, which around one in two people currently contract over the course of their lives and from which one in three die; lifestyle-related diseases such as diabetes, which are at the heart of most of the diseases directly affecting the health of citizens, and which are the main cause of cardiovascular disease; neuropsychiatric disorders, the number of patients suffering which is expected to grow with the progressive aging of the population, among other factors; and infectious diseases, regarding which all possible measures must be taken, in light of the globalization of society. In addition, they include cardiovascular diseases such as stroke, which accounts for the largest share of medical expenses and death rates by condition in Japan; respiratory diseases; musculoskeletal and connective tissue disorders, and urinary tract disorders; pediatric and perinatal diseases, which affect the next generation of citizens; infertility; HIV infection/AIDS, the number of new cases of which is increasing; hepatitis, which is the biggest infectious disease in Japan; immunologic allergic disorders, which reduce quality of life (QOL) over the long term; chronic pain disorders; rare and intractable diseases; the reduction or loss of physical function among elderly people and people with disabilities (including children with disabilities); health issues unique to women; diseases of the oral cavity, which are strongly suspected of being linked to lifestyle-related diseases; and addiction. Through these initiatives, the government will aim to create a society that promotes the development of technology that will assist in preventing the onset and exacerbation of these conditions, as well as preemptive medicine, new drugs and diagnostic and therapeutic techniques, and medical devices.

(c) Achieving medical care that makes full use of Japan's technical capabilities

Japan is a nation built on science and technology, so it is hoped that it will aim to become a country that develops the world's most advanced medical technology, making the fullest possible use of its remarkable problem-solving abilities in the field of engineering, materials science, and manufacturing, as well as regenerative medicine technologies and genome analysis, and can offer these to its citizens without delay.

(2) Improving industrial competitiveness in the field of drugs and medical devices

From 2001, the global market for medical care underwent sustained growth at an average rate of 8.7% annually, and was worth around ¥520 trillion in 2010. Amid this situation, Japan's trade deficit is growing (the trade deficit in the drugs and medical devices sectors was about ¥2 trillion in 2011.) On the other hand, looking at science and technology overall, Japan retains internationally competitive capabilities in basic

research and related technologies. Consequently, it is hoped that, as well as making use of this ability and extending it, efforts will be made to develop new drugs, medical device, and medical technology originating in Japan, which will contribute to our nation's economic growth.

(3) A country that promotes international medical collaboration and contributes to the international community

It is essential to contribute to efforts to improve medical care not only in Japan, but also in other countries, by developing new drugs, medical device, and medical technology originating in Japan. Initiatives focused on infectious diseases in developing countries will at the same time contribute to medical care and safety in our own nation.

Furthermore, it is expected that the Japanese medical technology and industrial competitiveness achieved through such activities will be utilized in efforts to combat global issues in partnership with various other countries, and that Japan will play a leading role in making an international contribution that takes advantage of our nation's strengths.

2. Issues Facing Japan

The fact that the outcomes of basic research are not always translated into drug discovery and practical diagnostic and therapeutic techniques, such as medical device, has been repeatedly pointed out over the years. The factors contributing to this can be identified at each of the relevant stages, namely basic research, clinical research and trials, industry, and research support systems offered by the government, etc.

(1) Issues facing basic research

In recent years, initiatives focused on basic research have also been enhanced in emerging economies such as China and South Korea, and such nations are rapidly catching up with Japan, the U.S.A., and Europe, so the relative international competitiveness of Japanese papers in the basic life sciences and clinical medicine is declining. Nevertheless, Japan retains a high level of international competitiveness in terms of its basic research capabilities.

There have been many cases in which product development resulted from the fact that the researcher conducting the basic research was themselves interested in development, or was based on knowledge identified in the research and development process within the pharmaceutical company. Thus, whether or not product development took place has conventionally been heavily dependent on the insight of the individual.

<Comparison of the Number of Papers Published by Country and Region in the Basic Life Sciences and Clinical Medicine>

(National Institute of Science and Technology Policy Research Material No.218: Benchmarking Scientific Research 2012)

Basic life sciences	No. of papers	Corrected no. of papers in top 1% cited
1999-2001	2nd worldwide	4th worldwide
2009-2011	5th worldwide	7th worldwide
Clinical medicine	No. of papers	Corrected no. of papers in top 1% cited
1999-2001	4th worldwide	8th worldwide
2009-2011	4th worldwide	14th worldwide

This Plan seeks to further enhance and strengthen such basic research capabilities, as well as encouraging translational research focused on the results of basic research. Until now, much basic research has gone no further than the presentation of papers, and although some pioneering projects have been implemented in relation to identifying the pathophysiology of diseases, drug discovery based on this knowledge, and research focused on translating the results of basic research into the development and practical application of medical device, overall there has not always been a great deal of activity in this area. This is thought to be due to both the lack of a strong desire on the part of researchers to feed the results of their research back into society and the lack of systematic management, with no system or experts capable of identifying promising seeds among research output and nurturing those with the potential to lead to practical applications.

(2) Issues facing clinical research and trials

From an international perspective, clinical research and trials in Japan still face many issues, so there is an undeniable tendency for pharmaceutical companies to conduct clinical trials at institutions overseas. One factor behind this has been the delayed response by the government to the fact that international standards for codes of ethics, data management, safety, and quality assurance in clinical research and trials have become more rigorous. The tendency for clinical research and trials to be conducted on a larger scale and to become prolonged has been spurred on by the requirement for rigorous data management and compliance with various regulations in such research

and trials, as well as by the fact that prognosis and such infrequent but serious phenomena as heart attack and stroke have come to be used as indicators of the effectiveness of drugs and medical devices. As a result, conducting clinical research and trials without substantial research funds and a strong research support system has become extremely difficult.

University hospitals have achieved numerous successes on the international stage in relation to their pathological studies of diseases, but adequate clinical research and trials have been lacking, due to the underdeveloped research system and personnel shortages. The national centers for advanced and specialized medicine (hereinafter “the National Centers”) have achieved some success in conducting clinical research and trials, taking advantage of their status as facilities that combine a hospital focused on the treatment of a specific group of disorders with a research institute focused on the practical application of treatment techniques. However, they cannot necessarily be said to have contributed to drug discovery and medical device development based on collaboration with companies.

Accordingly, efforts to improve case aggregation, increase the efficiency of clinical research and trial procedures, secure and cultivate researchers and experts, publish information about clinical research and trials, and improve the cost, speed, and quality required of clinical trials need to be reinforced.

(3) Issues facing industry

Japan is No.3 worldwide in terms of its achievements in drug development, but it has been pointed out that its impact in the development of innovative new drugs is declining, and that although Japanese researchers have been involved in the development of most of the world’s top-selling drugs, there is very little participation by Japanese companies when these drugs are commercialized.

The market for medical device is expected to grow in future, particularly in the field of diagnostic and therapeutic apparatus. However, entry into this field by Japanese companies is limited and their impact on this market is small compared with that of Western companies. Japan’s advanced manufacturing technology and the seeds of basic research in engineering at universities and colleges can be utilized in many fields, but the fact that such technologies have not necessarily been adapted to actual clinical needs can be cited as an issue.

Moreover, from the perspective of company scale, Japanese manufacturers of drugs and medical devices have fewer risk-tolerant management resources than their counterparts in the West. Furthermore, in recent years, companies have been investing

enormous sums in drug R&D, so the gap between Japan and the U.S.A. in terms of R&D expenditure per company is widening, due to the difference in company scale.

In Western countries, startup companies play a major role in drug discovery and the development of medical device. In contrast, Japan's environment for nurturing startup companies is underdeveloped, with a lack of venture capital to supply risk capital, as well as a shortage of personnel with the relevant expertise. Coupled with a structure in which there are few people who actively want to take risks in managing such companies, the role played by startup companies remains limited.

Furthermore, not all companies necessarily have a good awareness of the reality of medical care or of unmet medical needs. This appears to be one factor behind Japan's lack of adequate data indicating the actual situation regarding medical care and diseases, which forms the basis of research and development, as well as behind the lack of adequate communication and people-to-people exchange between the researchers aspiring to drug discovery and those working in clinical settings (although this is not an issue exclusive to companies.)

(4) Issues facing the research support system

Until now, government ministries have pursued medical R&D from their own individual standpoints, with the Ministry of Education, Culture, Sports, Science and Technology focusing on the stage from basic research through to nonclinical tests, while the Ministry of Health, Labour and Welfare has focused on the stage from clinical research and trials through to practical application and the Ministry of Economy, Trade and Industry has promoted research from the perspective of revitalizing industry. As such, collaboration between them has undeniably been inadequate. Consequently, the construction of a system that enables R&D to be conducted seamlessly from basic research through to practical application, making effective use of limited budget resources and personnel, has become a pressing issue. Moreover, as well as considering the flexible use of public research funds, efforts should be made to utilize the donation tax system, which has been revised to facilitate the effective use of funding from the private sector.

3. Basic Policy

The basic principle underlying advanced R&D in the field of healthcare and medical care in Japan is, as stated in the basic principles of the Act on Promotion of Healthcare Policy, to contribute to the provision of the world's best medical care medical care by promoting integrated medical R&D activities, from basic R&D to R&D focused on

practical applications, and by facilitating the practical application of the results of these activities.

In light of this principle, as well as the background to and current status of medical R&D as described in I. 2, the following measures shall form the Basic Policy on Medical R&D.

- (a) Building systems that lead to the practical application of the results of basic research
- (b) Building new mechanisms for developing drugs and medical devices
- (c) Initiatives aimed at the establishment of evidence-based medicine
- (d) Utilizing and promoting the use of information and communications technology (ICT) focused on health and medical information
- (e) Initiatives for achieving the world's most advanced medical care
- (f) Initiatives based on international perspectives
- (g) Human resource development
- (h) Fair research mechanisms and improving the environment to ensure ethical, legislative, and regulatory compliance
- (i) Developing the research base
- (j) Intellectual property management initiatives

II. Intensive and Systematic Medical R&D Measures

1. Initiatives Required to Resolve Issues

Academia, medical institutions, industry, the national government, and local governments must work in partnership while implementing the following initiatives, focusing on the long-term perspective while also aiming to achieve results in the shorter term.

(1) Building systems that lead to the practical application of the results of basic research

To sustain medical R&D, it is necessary to strengthen basic research and constantly generate groundbreaking seeds. Fundamental improvements in the environment for conducting clinical research and trials, and innovation aimed at the creation of drugs and medical devices originating in Japan are the key to translating the results of basic research into practical applications.

(a) The need to fundamentally improve the clinical research and trials environment

In some countries, centers with thousands of beds have been established to enable intensive clinical research and trials to be conducted in a single location. In Japan, on the other hand, efforts have focused on building a network of multiple centers, and clinical research and trials are being promoted through the development of ARO (Academic Research Organization) functions based in the centers being created as part of the Project for Japan Translational and Clinical Research Core Centers (translational research support centers, centers for early and exploratory clinical trials, core hospitals for clinical research, and centers for Japan-led global clinical research (hereinafter “Innovative Medical Technology Creation Centers”)) and National Centers. To advance clinical research and trials, a mechanism for ensuring the implementation of high-quality world-class clinical research and trials must be built. This should be done not only by seeking to consolidate cases between facilities, but also by promoting the following additional improvements in function while making effective use of these resources. More in-depth consideration of the approach to be taken by the National Centers in Japan’s medical R&D is also required.

(i) Improving the quality of clinical research

It is necessary to improve the quality of clinical research, including improving case aggregation, cost, and speed, and promoting the ICH-GCP (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use – Good Clinical Practice) standards. Accordingly, quality control and

quality assurance must be carried out through such practices as the preparation of source documents based on the ALCOA principles, as well as monitoring and auditing. One means of responding to these requirements is to utilize the ARO functions of Innovative Medical Technology Creation Centers, which will serve as bases for various networks, as well as the functions of central ethical review boards and institutional review boards. In addition, integrated management of individual clinical research and trials would be effective, focusing on efficient implementation of R&D management, such as the formulation of research protocols, updates on the progress of research, management of research data (data input, collation, and analysis), and management of research results and intellectual property. It is anticipated that this will also lead to greater efficiency in clinical research and trial procedures. In addition, to strengthen partnerships between the PMDA (Pharmaceuticals and Medical Devices Agency) and universities, research institutes, medical institutions, and companies, with a view to ensuring that research results are linked efficiently to pharmaceutical approval, it will be necessary to enhance the pharmaceutical affairs consultation system and make the requisite operational improvements to the priority clinical trial consultation system.

(ii) Cultivating researchers and experts, and securing personnel

Japan's basic research papers in the field of medical science are beginning to be comparatively highly regarded, so Japan has a substantial international presence in this area. On the other hand, when it comes to papers concerning clinical research and trials, our nation's international presence is lower and is actually declining further. Improvements in both the quality and quantity of clinical research and trials are required, with this domain being positioned as an important part of medical science. To do so, Japan must first establish career paths that will attract personnel involved in clinical research and trials. In particular, it is necessary to enhance the education provided to undergraduates in the field of medicine and pharmaceutical sciences concerning clinical research and trials, and to cultivate young researchers by such means as establishing posts in which they can conduct such research and trials.

In addition, cultivating and securing biomedical information science personnel, working in such fields as biostatistics, bioinformatics, and big data analysis, is essential to future efforts to promote clinical research and trials that utilize genetic and medical information.

Furthermore, the role played by experts in the fields of epidemiology, bioethics, and research ethics is absolutely crucial. There is a shortage of such personnel at present, so securing and cultivating such human resources without delay is vital.

(iii) Shared use of common infrastructure for clinical research and trials

Centers across the country will share access to such infrastructure as CPCs (Cell Processing Centers), which process large quantities of cells for use in clinical research and trials, as well as equipment that facilitates production management and quality control in accordance with GMP (Good Manufacturing Practice) standards. Furthermore, it is necessary to promote shared use of special advanced research infrastructure, such as technology used for analyzing genetic information, as well as other cutting-edge measurement and analysis technologies.

(iv) Efforts to prevent research irregularities and misuse of research funds

In recent years, problems have emerged in relation to the manipulation of data and conflict of interest in a research paper concerning an antihypertensive drug. To ensure that such acts do not occur again, it is essential to implement thorough initiatives to ensure compliance not only in administration, but also in R&D environments. These include the publication of information regarding clinical research, as well as auditing, monitoring, management of conflicts of interests, and research ethics education targeting physicians, pharmacists, and researchers, both before and after graduation.

(v) Initiatives focused on patient collaboration and raising awareness among citizens

In conducting clinical research and trials, it is necessary to ensure collaboration with test subjects and patients, as well as actively promoting activities to raise awareness among patients and the populace as a whole regarding the significance of clinical research and trials, as well as the benefits they bring to citizens. In particular, initiatives at university hospitals and National Centers, whose mission is education and research, need to be considered.

Accordingly, the government will implement the following measures.

<Interministerial collaborative projects (initiatives compiled by the Headquarters for Healthcare Policy on August 30, 2013)>

- Project for Japan Translational and Clinical Research Core Centers (described below in II. 2. (2))

- Nurturing young researchers

- At translational research support centers, the government will promote education and on-the-job training concerning translational research, targeting students and young researchers.

- To nurture support staff for clinical research and trials, so that high-quality clinical research and trials can be implemented, training for entry-level clinical research coordinators (CRCs), senior CRCs, and data managers (DMs) will continue, along with training for ethical review board members, with the aim of cultivating more than 500 senior CRCs by FY2016. In addition, the government will aim to launch in FY2015 (i) training for physicians involved in clinical research and trials, and (ii) efforts to coordinate the eligibility requirements for examinations targeting senior CRCs certified in the private sector, as well as the content of those examinations.

<Measures other than interministerial collaborative projects>

- Enhancing pharmaceutical affairs consultations with a view to the effective use of research results

- At the PMDA, the government will aim to enhance the pharmaceutical affairs consultation system by providing consultation services that offer advice regarding the development process (roadmap) and protocols for confirmatory trials. Furthermore, it will seek to reflect the needs of those seeking guidance by enhancing the fields on which pharmaceutical affairs consultations and other clinical trial consultation services focus, including matters concerning reliability criteria, and will also improve the types of consultation available.

- Nurturing young researchers

- The government will support university initiatives to cultivate personnel capable of promoting medical innovation, equipped with the ability to lead the world's most advanced R&D and to facilitate the spread of the results thereof in future, both within Japan and overseas.

- The government will position education concerning clinical research and trials as part of the model core curriculum, which sets out guidelines for the content of education in medical and pharmaceutical sciences, and will encourage all universities to implement initiatives in this area.

- Securing and cultivating personnel in the field of biomedical information science

- As well as aiming to enable researchers in the field of biomedical information science

to secure careers by promoting R&D focused on the advanced ideas of young researchers and students, the government will provide support for research and education at universities, etc.

- Promoting appropriate implementation of statistical analysis and monitoring in clinical research
 - Under the Ethical Guidelines for Clinical Studies, which are currently under review, principal investigators will, in future, be required to conduct monitoring and auditing. In addition, the government will aim to put in place from FY2015 the systems required for monitoring at institutions conducting clinical research.

- Deliberations concerning legislative measures
 - With a view to restoring trust in Japanese clinical research, the government will move forward with the review of the Ethical Guidelines for Clinical Studies, taking into account the report by the Investigative Committee on the Incident Involving Clinical Research into an Antihypertensive Drug, and will aim to begin considering approaches to systems related to clinical research, including the legal system, by the autumn of 2014.

- Promoting efforts to raise awareness
 - Information about clinical research and trials is provided at the National Institute of Public Health's NIPH Clinical Trials Search site. This site will be revamped in FY2014 to make it easier for patients and other citizens to use, with improved search functions. In addition, its existence will be publicized, to promote greater use of the site.
 - Among specific groups of disorders (such as cardiovascular disorders) are some diseases regarding which it can be difficult to compile details of specific cases. To further promote clinical research and trials focused on these, the government will devote greater efforts to building networks encompassing the facilities specializing in the study of each particular condition, with the National Centers serving as the focal point of these, and to developing patient record systems. The government will aim to ensure that these are operating in six centers by FY2017.

(2) Promoting “cyclical R&D” and achieving open innovation

(i) In relation to translational research (TR), it is important not only to link the results of basic research to clinical settings, but also to carry out reverse TR, which feeds issues identified in clinical settings back into basic research. This will become possible

through epidemiological and clinical epidemiological studies focused on numerous cases. This cyclical approach will focus not only on new diagnostic and therapeutic techniques, but also on existing ones, and will become the basis of medical R&D.

(ii) Development costs have soared in recent years and it is becoming difficult for a single company to conduct medical R&D alone. Accordingly, it is increasingly important for universities, research institutes, hospitals, and companies to form networks and work in partnership with each other. As well as setting themes that take into account the most effective means of applying limited budgets to medical care and the medical care industry, it is necessary to undertake initiatives that achieve open innovation, while ensuring that intellectual property is secured.

(iii) To strengthen collaboration between industry, academia and government and promote research into practical applications, as well as technology development, it is vital to form consortiums and cultivate next-generation industries by promoting open innovation based on collaboration between industry, academia and government. Securing the necessary financing through various funds, and supporting SMEs and startup companies are also important. Moreover, there is a need to improve efforts to encourage industrialization in the field of medical care.

(iv) The government will strengthen the partnerships forged by the PMDA with universities, research institutes, medical institutions, and companies. In addition, it will seek to disseminate and enhance regulatory science (science that forms the basis for research concerning the evaluation of effectiveness and safety, and the establishment of guidelines for development and review) in R&D by augmenting the pharmaceutical affairs consultation system, developing examination guidelines, and improving the specialist knowledge of examiners. In addition, it is necessary to enhance and strengthen support for drug discovery and the development of medical device, including the establishment of consultation services, approval reviews, and post-approval safety measures to facilitate appropriate responses aimed the practical application of innovative drugs and medical devices. To this end, the PMDA will be involved in the development process from an early stage, looking ahead to the exit strategy in R&D.

(v) To support R&D based on regulatory science, the PMDA and National Institute of Health Sciences must actively engage in people-to-people exchange with universities, etc.

Accordingly, the government will implement the following measures.

- Support for R&D provided by the Drug Discovery Support Network to promote new drug discovery
 - Through the Drug Discovery Support Network, the government will support R&D focused on new drug discovery, working in partnership with universities and industry.
 - The government will move forward with efforts to enhance the infrastructure for innovative research, with a view to strengthening the Drug Discovery Support Network.

- Establishing a Medical device Development Support Network
 - To encourage the development of medical device via collaboration between medicine and industry, the government will establish a system that will enable multiple specialist support organizations to support the development of such medical device (the Medical device Development Support Network (tentative name)).

- Provision of finance via various funds and support for SMEs and startup companies
 - The government will nurture industries within the field of healthcare and medical care by offering support for business expansion, etc. to startup companies and SMEs, using both finance from public-private investment funds and finance from relevant organizations.

- Promoting industrialization in the field of medical care
 - With a view to the practical application of the research results of universities, etc., the government will provide support for everything from the identification of promising seeds to the development of practical applications by corporate entities, and for joint research by industry and academia focused on the results of outstanding basic research or on themes that will contribute to the resolution of technical issues faced by industry.

- Promoting regulatory science
 - The government will conduct research concerning techniques for evaluating the side-effects of nucleic acid medicine, which is being pioneered in Japan ahead of the rest of the world, as well as developing new official quality testing techniques adapted to cutting-edge technologies and new safety testing methods such as those that use alternatives to animal testing.

- Strengthening collaboration by the PMDA and the National Institute of Health Sciences with universities and research institutes, etc.

- The government will cultivate personnel well-versed in regulatory science through people-to-people exchange between universities, etc. that are conducting the world's most advanced research, and the PMDA and National Institute of Health Sciences. In addition, it will compile guidelines for the development and evaluation of innovative drugs, medical devices, and regenerative medicine products, etc.

- Supporting drug discovery and medical device development through consultation services, approval reviews, and post-approval safety measures

- The PMDA itself will strive to improve the quality of its reviews and consultation services by conducting research and analysis that utilizes data concerning clinical trials. Moreover, it will improve the environment with a view to utilizing medical information databases in safety measures. In addition, in terms of the PMDA's own operations, it will aim to achieve a review lag of zero by 2020, and will strengthen the requisite systems in order to improve the quality of reviews and strengthen safety measures.

- To accelerate the practical application of innovative drugs, medical devices, and regenerative medicine products, etc., the government will offer pharmaceutical affairs consultation services and conduct GMP studies via the West Japan branch of the PMDA (PMDA-WEST), and will strive to improve the predictability of its approvals for drugs and medical devices.

- Consideration will be given to further expanding the scope of acceptance of English-language materials among the supporting materials submitted when applying to the PMDA for approval for a new drug.

(2) Building new mechanisms for developing drugs and medical devices

- To build a system for unearthing and adopting promising seeds within Japan and link these into practical applications, it is necessary to develop systems for promoting integrated R&D activities, from basic R&D to clinical research and trials, and on to practical applications, as well as for assisting verification in clinical settings and the identification of new challenges.

In doing so, it is vital to develop an intellectual property strategy focused on the exit point from R&D, identify seeds with a high potential for practical application among the results of basic research, and aggregate and utilize data concerning clinical research and trials in order to smooth the path for translating basic research into applied research, clinical research and trials, and ultimately practical applications. Moreover, to

encourage the practical application of innovative drugs and medical devices originating in Japan, greater efficiency, speed, and use of regulatory science must be promoted by cultivating personnel with advanced knowledge and skills in a wide range of fields, and laying the foundations for the development of drugs and medical devices. Furthermore, it is necessary to expedite R&D and reduce the cost thereof by utilizing ICT (Information and Communication Technology), including the construction of databases and the analysis of big data for registry studies that record routine clinical cases.

To ensure that clinical research and trials are conducted efficiently within a short period of time, with a view to ensuring the prompt implementation of clinical research and trials of all kinds, including First in Human trials for new drug development, an environment conducive to the aggregation of cases must be put in place, so that networks encompassing the Innovative Medical Technology Creation Centers and National Centers can be strengthened and internationally-recognized clinical research and trials can be carried out.

University startups and other startup companies have a crucial role to play in the development of drugs and medical devices.

To support the development of practical applications, the PMDA's systems for pharmaceutical affairs consultation, etc. must be strengthened. In addition, there is a need to formulate and provide advice concerning an exit strategy for promising seeds in partnership with the PMDA, and to strengthen business partnerships and collaboration support functions, including the provision of information to companies and business matching.

Based on this awareness, the government will undertake the following initiatives in the respective fields of drugs and medical devices.

(a) Drugs

Efforts must be made to ascertain patient needs and set strategic themes, in order to accelerate the development of innovative drugs originating in Japan. In terms of the target technologies, it will be necessary to focus on new drug discovery resources in the form of nucleic acid, antibodies, vaccines, and stem cells, as well as conventional drug discovery resources in the form of low molecular weight compounds and natural products. Furthermore, it must be noted that great progress is being made in the molecular design of drugs, due to advances in structural biology aimed at using molecular structure to understand the molecular function of biopolymers, with a particular focus on proteins.

To foster drug discovery, an environment must be put in place that facilitates efforts

to search for seeds among research results from academia, and which makes it easier for researchers in various fields to make use of research support infrastructure related to drug discovery. Accordingly, the government will utilize the Drug Discovery Support Network and other bodies to support the search for seeds, intellectual property management, and the applied research required for practical application. Moreover, it is necessary to look at building a research system aimed at drug repositioning by conducting comprehensive efficacy profiling of existing medications and compounds demonstrating new pharmacological actions whose development has been discontinued, and identifying new target molecules in order to search for new indications and develop these medications as drugs with new effects. Furthermore, initiatives are required that focus on blending nanotechnology with systems that control the delivery of drugs within the body in terms of quantity, space, and time (drug delivery systems: DDS).

In addition, there is a need to promote research that emphasizes such international standards as GLP (Good Laboratory Practice) and GMP from the outset, along with regulatory science, which seeks to ensure quality, effectiveness, and safety. Simultaneous development of companion diagnostics, which forecast the effects or side-effects of molecular target drugs, and efforts to optimize the design of clinical research and trials must also be promoted.

Accordingly, the government will implement the following measures.

<Interministerial collaborative projects>

- Project for Drug Discovery and Development (described below in II. 2. (2))

- Support for R&D offered by the Drug Discovery Support Network to promote new drug discovery (described above: II. 1. (1) (a))

- Using drug repositioning to promote the development of drugs to treat rare diseases
 - Through the promotion of research into the development of evidence demonstrating new therapeutic effects in existing drugs (drug repositioning), the government will promote the creation of drugs originating in Japan that assist in conquering intractable and rare diseases, and will aim to license these out to companies by 2020.

- Blending drug delivery systems with nanotechnology
 - The government will implement innovative technology development focused on

tissue-specific drug delivery systems, with a view to the utilization of nanotechnology.

- Promoting simultaneous development of companion diagnostics in personalized medicine, etc. and optimizing the design of clinical research and trials
 - The government will promote research into techniques for evaluating companion diagnostics in conjunction with drug reviews. In the case of new drugs in particular, it will put in place a system for simultaneous review with companion diagnostics, as a general rule. In these initiatives, the government will aim for licensing out to companies by 2020.

- Promoting programs to encourage drug development via joint public-private initiatives
 - The government will identify the challenges that must be dealt with to eliminate obstacles to drug development in Japan; for each challenge, it will establish a technology research group with the participation of individuals from academia, pharmaceutical companies, and National Centers, etc., which will build systems for promoting intensive research, with the aim of achieving results within five years.
 - The government will promote joint research by pharmaceutical companies and the National Institute of Health Sciences focused on quality risk assessment and product quality control to accelerate the development of innovative antibody preparations, as well as research into the development of biomarkers that can be used for early and advance diagnosis of side-effects, aiming to achieve results within five years.

<Measures other than interministerial collaborative projects>

- Promoting regulatory science (described above: II. 1. (1) (a))

- Developing drugs to treat rare diseases that have a particularly small number of sufferers
 - In promoting R&D of drugs and medical devices to deal with rare diseases, the government will begin by focusing on areas where R&D needs to be accelerated. As part of this, in 2015, it will begin targeted support for research into what are called “ultra orphan drugs,” which treat diseases that have a particularly small number of sufferers.

- Appropriate evaluation of innovation

- To advance the development of innovative drugs and medical devices in Japan, the government will seek appropriate evaluation of innovation within the prescription drug price system, etc.

(b) Medical device

In conducting initiatives in the field of medical device, it is necessary not only to support the development of cutting-edge medical device by developing clinical applications for completely new basic technological seeds, but also to support the development of a wide range of medical device and peripheral technologies originating in Japan, by passing on and further advancing Japan's sophisticated skills in manufacturing, keeping in mind the exit point from the R&D process.

R&D tailored to clinical needs and efforts to improve, modify, and optimize in clinical settings are extremely important when it comes to medical device. It is absolutely vital to facilitate the acceleration of the applied research and prototype development process, and to ensure an appropriate transition into the practical application of medical device following evaluation in clinical settings. To this end, medical institutions such as university hospitals and National Centers will be charged with responsibility for measures aimed at matching basic technological seeds at universities, etc., common basic technologies such as advanced measurement and analysis technologies, and the sophisticated manufacturing technologies of SMEs with needs in clinical research. In addition, they will be responsible for the establishment of R&D centers with direct links to clinical research. Accordingly, the following measures will be required.

(i) Identification of needs in clinical research and seeds expected to lead to practical applications, formulation of R&D projects via selection and concentration, and establishment of a system for implementing these

(ii) Improvement and optimization of existing medical device, enhancement of mechanisms to enable clinical institutions to conduct clinical research and trials in partnership with medical device manufacturers, improvement of existing medical device that is expected to have practical applications in the short term, and promotion of medical device development via appropriate matching of needs in clinical research with basic technological seeds at universities, etc. and technological seeds among the advanced manufacturing technologies of SMEs

(iii) Initiatives focused on relatively high-risk therapeutic instrument technologies (instruments that combine therapeutic techniques with the diagnostic techniques in which Japan's strengths lie, as well as minimally invasive diagnostic and therapeutic instruments), advanced diagnostic techniques, robot technology, and cutting-edge diagnostic and therapeutic instrument technologies, such as heavy ion radiotherapy devices.

(iv) Establishment of a support system to increase the efficiency of medical services and reduce their cost, via the effective use of technology that blends ICT with robot technology

(v) Development of mechanisms for cultivating personnel capable of identifying actual needs in medical care, and initiatives focused on the exchange of personnel in the fields of medical care and development

(vi) Establishment of strategies for commercialization, pharmaceutical affairs (including the swift, accurate gathering and evaluation of evidence concerning effectiveness and safety in nonclinical tests and clinical trials), and intellectual property in development, and the creation of networks that will facilitate collaboration between relevant organizations to provide various forms of support that will contribute to successful development

(vii) Constructing platforms for improving international industrial competitiveness, as well as ensuring ongoing strengthening of development capabilities

(viii) Initiatives focused on developing medical device to support the physical functions of elderly people and people with disabilities

Accordingly, the government will implement the following measures.

<Interministerial collaborative projects>

- Establishing a Medical device Development Support Network (described below in II. 2. (2))

- Enhancing mechanisms to enable clinical institutions to conduct clinical research and

trials in partnership with medical device manufacturers, and conducting appropriate matching of needs with seeds

- Personnel from companies developing medical device will be hosted at medical institutions conducting medical device R&D, to further improve the organization at medical institutions developing medical device. In conjunction with this, the medical institutions in question will promote development of medical device that meets medical needs both within Japan and overseas.

- To encourage new entry to the field of medical device by SMEs in the manufacturing sector, the government will support the dispatch of the requisite experts when support organizations with strong roots in the community provide matching services.

- Promotion of the development of cutting-edge diagnostic and therapeutic instrument technology

- The government will promote R&D through academic-industrial collaboration focused on cutting-edge diagnostic and therapeutic equipment and systems, such as relatively high-risk therapeutic instruments and new diagnostic instruments, with a view to clinical research and trials, and practical applications.

- Establishing a support system to increase the efficiency of medical services and reduce their cost

- The government will promote R&D focused on treatment support systems that enable the optimal treatment to be provided, by searching and analyzing past data concerning the treatment of similar cases.

- Considering mechanisms for cultivating personnel capable of identifying needs in medical care

- Within five years, the government will consider mechanisms for cultivating personnel capable of identifying medical needs, by hosting personnel from companies developing medical device at medical institutions conducting R&D, so that these personnel can provide training in product design methods focused on marketability. As part of these deliberations, the government will consider the compilation of a program for such training.

- Exchange of personnel in the fields of medical care and medical device development

- The government will promote people-to-people exchange among medical personnel and personnel working on the development of medical device. To this end, it will

arrange training courses and an annual seminar for those involved in medical device development at medical device companies and medical institution. Those with experience in the development of medical device, the review of such device, or drug regulatory affairs will be invited to give lectures at such events.

- Development of equipment to support the physical functions of elderly people and people with disabilities, etc.

- The government will promote the development of technology – including the use of communication support equipment and devices that apply knowledge from the field of neuroscience, as well as robot technology – that will help to remove social barriers, so that elderly people and people with disabilities can have peace of mind while living in their local communities. It will aim to ensure the practical application of at least three functional support devices within five years.

- Development of home medical care equipment

- The government will promote the development of home medical care equipment, taking into account the needs of staff providing home medical care. Moreover, in terms of measures to deal with stroke and other cardiovascular disorders that are the main triggers of the need for nursing care, the government will promote the development of portable medical device, with a view to facilitating home medical care in the future, aiming to license out such device to companies by 2020 at the latest.

- Development of robotic care equipment

- To promote greater self-reliance among elderly people and people with disabilities, and alleviate the burden on those providing nursing care, the government will develop robotic care equipment tailored to frontline nursing needs, and will put in place an environment conducive to the introduction of such equipment, by such means as the formulation of standards for safety, performance, and ethics.

<Measures other than interministerial collaborative projects>

- Promotion of the development of cutting-edge diagnostic and therapeutic instrument technology

- The government will promote R&D focused on making heavy ion radiotherapy apparatus smaller and more sophisticated, as well as R&D with a view to the overseas deployment of such technology.

- To reduce the risks of radiological diagnosis and treatment instruments and ensure that they can be used with peace of mind, while still offering benefits to the patient, the government will promote surveys and R&D concerning medical exposure.

- Regarding molecular imaging technology, the government will promote the development of radiopharmaceuticals, such as probes for use in PET, and bioinstrumentation, as well as promoting basic research in such areas as pathological diagnosis and treatment.

- Appropriate evaluation of innovation

- To advance the development of innovative drugs and medical devices in Japan, the government will seek appropriate evaluation of innovation within the prescription drug price system, etc. (Described above: II. 1. (2) (a))

(3) Initiatives aimed at the establishment of evidence-based medicine

Evidence-based medicine, which takes into account not only the understanding of a disease based on the causal relationship at the molecular level, but also environmental and genetic factors, has grown in importance in recent years. Accordingly, initiatives that utilize objective data are required, in order to strengthen international competitiveness in clinical research and trials. In evaluating drugs, medical devices, etc. and medical technology (technology required to provide medical care; excludes drugs (drugs as stipulated in Article 2 (1) of the Act on Ensuring the Quality, Effectiveness, and Safety of Drugs and Medical devices, etc. (Act No. 145 of 1960. Hereinafter referred to in this plan as the “Drugs and Medical devices Act”), medical device (medical device as prescribed in paragraph 4 of said Article), and regenerative medicine products, etc. (regenerative medicine products, etc. as prescribed in paragraph 9 of said Article). The same shall apply hereinafter in “II. Intensive and Systematic Medical R&D Measures”), interventional clinical research and trials are the most important. However, registry studies are just as important as intervention studies, so it is necessary to improve infrastructure and develop information technology to promote them.

In particular, as efforts to elucidate the relationship between genetic information and diseases and drug efficacies have progressed, due to advances in large-scale genome analysis technology, biobanks, which have high-quality samples accompanied by ample clinical information, and epidemiological studies can make an increasingly important contribution at each stage, including disease prevention, the selection of treatment methods, and prognosis. In Japan, initiatives focused on building up large-scale cohorts and banks not only of patients, but also of healthy individuals for various purposes have

been underway in each region for some time, so it is necessary to use these to create a network and to ensure that they are utilized effectively. Given the wide-ranging and large-scale nature of such samples and information, their integration is vital. Once this has been done, support will be required in dealing with bioethical issues and disease specimen banks will need to be developed, to ensure effective use of clinical information, as well as diseased tissue and other samples obtained from patients. In addition, it will be necessary to consider enabling companies, etc. to access anonymized data.

Moreover, in setting out the priority research fields for medical research, adequate consideration is required to ensure that conventional grassroots research into diseases and epidemiological studies are not neglected.

Although a large, diverse array of treatments exist in the field of integrated medical care, it would be fair to say that the overall level of scientific knowledge in this area is not adequate at present. Accordingly, knowledge concerning safety and effectiveness must be gathered and techniques for its evaluation established.

Accordingly, the government will implement the following measures.

<Interministerial collaborative projects>

- Japan Genomic Medicine Project (described below in II. 2. (2))

- 1) Establishing digital infrastructure in the fields of medical, nursing and health care, including the development and linkage of database functions (described below in II. 1. (4))

- (4) ICT initiatives

In terms of the application of ICT to Japanese health and medical information to facilitate its effective use in R&D, it would be fair to say that appropriate digitization and organic integration have not been carried out. Accordingly, practical database functions – including the use of big data from electronic medical records and other ICT – must be enhanced without delay. In doing so, it is necessary to devise ways of promoting the effective use of such medical information and to put in place social rules that will ensure that all citizens can enjoy the benefits of this.

Section II. 1. (1) (a) (i) describes the key initiatives focused on improving case aggregation with a view to implementing efficient clinical research and trials. In

addition, technology capable of integrating citizens' medical information, health check information, and information from medical receipts in a more flexible format will need to be installed, along with the standardization of data formats and disease classifications, and the establishment of operational rules without delay.

As the application of ICT to medical information progresses, it will be vital to consider and put in place conditions concerning the handling of medical information when providing it to third parties so that it can be used in research. In these deliberations, the need for legislative amendments must be considered.

There is also a need to promote R&D focused on the comprehensive application of ICT in medical care, including R&D concerning technologies that assist in telemedicine and home medical care, the development and use of biomedical simulation technology, the utilization of data analysis technology for bringing genomic medicine to fruition, and greater use of digital technology in history taking, diagnosis, surgery, and treatment. In addition, efforts to ensure the interoperability of systems handling such medical information are required.

Accordingly, the government will implement the following measures.

- Establishing digital infrastructure in the fields of medical, nursing and health care, including the development and linkage of database functions
 - The Headquarters for Healthcare Policy will be at the heart of efforts to build digital infrastructure that incorporates into a single package mechanisms for ensuring interoperability and portability, which will enable the necessary data to be consolidated from information systems in the fields of medical care, nursing care, and healthcare, according to the purpose of its use, and systems for comprehensively promoting and coordinating such mechanisms. In doing so, the Headquarters will collaborate with the IT Strategy Council and relevant ministries and agencies in undertaking the cross-sectoral deliberations required for efficient, effective use of ICT in projects focused on the gathering and analysis of data from medical information, to ensure the interoperability of systems and portability of medical information between such systems. More specifically, the government will promote integration to the maximum extent necessary and possible, and will seek to enhance the functions of databases, etc., with a view to facilitating the gathering of information from databases, the nationwide roll-out of regional information-sharing infrastructure, and the sharing of information in home medical care and nursing care.

- Upgrading academic information networks
 - The government will upgrade academic information networks to ensure interoperability between systems handling medical information.

- Promoting R&D and demonstrations concerning the comprehensive application of ICT in medical care
 - To ensure efficient, high-quality diagnosis and treatment throughout each hospital via the utilization of ICT, the government will promote R&D and practical application in relation to next-generation medical device and hospital systems using ICT. In conjunction with this, as well as examining R&D systems, it will consider systems for promoting widespread use, which will be vital to R&D in the field of medical ICT.

- Developing more advanced simulation technology
 - Through simulations using state-of-the-art supercomputers such as K computer, the government will strive to bring innovative medical care to fruition. For example, the Cardio Simulator, which replicates everything down to the molecular level, will be used to consider therapies and evaluate the effects of drugs by shedding light on the pathology of intractable diseases.

- Upgrading the handling of medical information, etc.
 - Assuming that public acceptance is forthcoming, efforts will be made to enhance the handling of medical information by considering effective use of numbering systems in fields such as medical care, and clarifying the social rules for the use of medical information. In addition, the government will design sustainable data usage systems that utilize the dynamism of the private sector.

(5) Initiatives for achieving the world's most advanced medical care

Given its status as an advanced country in the field of science and technology, Japan should prioritize the key challenge of R&D aimed at achieving the world's most advanced medical care, in the form of regenerative medicine and genomic medicine.

Basic research also has an important role to play in the development of such state-of-the-art medical care. Although Japan remains internationally competitive in terms of its basic research capabilities, multidisciplinary research must be promoted, without neglecting investment in basic research, in order to ensure that our nation can continue to create innovative seeds that demonstrate outstanding ability to meet medical needs. In addition, it is vital not only to ensure a smooth flow from basic research into

clinical studies, but also to facilitate close communication of feedback between the two elements, so simultaneous support for both elements is required. In addition, partnership and cooperation with pharmaceutical companies, which have resources and technologies such as compound libraries, is essential in developing practical applications for drugs discovered in academia. Accordingly, ongoing support for academic-industrial collaboration is required.

In conducting such initiatives, it is necessary to not only steadily promote R&D, but also to simultaneously undertake deliberations aimed at dealing with issues and risks that emerge precisely because of the pioneering nature of such R&D, as well as ensuring that society is ready to accept such innovations.

Furthermore, in linking the results of basic research to the exit point, such research must from the outset be promoted in tandem with systematic, strategic initiatives, including intellectual property rights, based on work schedules that clarify the exit strategy in light of the needs of patients and the rest of the populace. In addition, objective evaluation must be carried out as such research progresses.

(a) Bringing regenerative medicine to fruition

Given that regenerative medicine products, etc. differ in nature from drugs and medical devices, an approval system based on their distinctive attributes has been established in the Act on Ensuring the Quality, Effectiveness, and Safety of Drugs and Medical devices, etc. (Act No. 145 of 1960), to ensure the swift, safe provision of regenerative medicine to the populace. In addition, the Act to Ensure the Safety of Regenerative Medicine, etc. (Act No. 85 of 2013) prescribes procedures for the harvesting of cells, standards for medical institutions providing regenerative medicine, etc., and standards for facilities cultivating and processing cells, to ensure the safety of regenerative medicine treatment. Amid this situation, to maintain Japan's superiority in the field of regenerative medicine and drug discovery research using iPS cells and other stem cells, everything from basic research into iPS cells to applied research, clinical research and trials, and practical applications in this area must continue to be selectively promoted, along with efforts focused on identifying the pathophysiology of diseases. In addition, academic-industrial collaboration in the development of automatic mass culture apparatus and peripheral devices ahead of the rest of the world is required, taking advantage of the technology in which our nation excels. Moreover, domestic systems for the large-scale, stable production and supply of materials used in regenerative medicine are essential in order to move on to the next phase from basic research, so it is necessary to promote academic-industrial collaboration projects

focused on building manufacturing and quality control systems that are consistent with international standards. To promote the banking of iPS cells and allogeneic cell transplantation therapies, efforts must be made to accelerate everything from basic research to applied research, clinical research and trials, and practical applications for such therapies.

As well as the fact that the process from nonclinical tests through to the granting of approval for manufacture and sale takes a long time, regenerative medicine products, etc. involve numerous manufacturing processes and extremely sophisticated hygiene management, and tests and inspections of such products cost a great deal of money. Accordingly, an integrated support system that offers seamless long-term support – including the proactive use of advice from the PMDA’s pharmaceutical affairs consultation service – is required. Consequently, government ministries need to work together, offering integrated support that links their respective achievements into basic research, applied research, clinical research and trials, and practical applications.

At the same time, regulations tailored to systems for the manufacture and supply of products are required, to maintain credibility and international competitiveness. Accordingly, it is necessary to build a system for conducting tests and inspections to ensure a high level of quality.

In addition, to ensure that the time and money spent on development are not wasted, it is necessary to formulate standards for iPS cell stock and other raw materials used in regenerative medicine products, etc., as well as standards for drug evaluation techniques using iPS cell-derived differentiated cells and associated clinical research and trials. As well as international coordination and negotiation regarding the international standardization of drug evaluation techniques, efforts to ensure consistency are also required in order to promote widespread overseas use iPS cells and differentiated cells originating in Japan.

There are various ethical, legal and social implications involved in the clinical application of human iPS cells, so discussions need to include society as a whole, rather than just researchers, to carefully build consensus.

Moreover, it is vital to strengthen not only regenerative medicine, but also drug discovery research using iPS cells. Collaboration between industry, academia and government is needed in developing technology for the establishment of disease-specific iPS cells (such as those for use in treating intractable diseases), and for cell stock and analysis methods, as well as research into diseases and drug discovery research using these. In doing so, it is necessary to ensure a seamless, consistent path from basic research through to applied research, clinical research and trials, and

ultimately practical application.

Accordingly, the government will implement the following measures.

<Interministerial collaborative projects>

- Japan Regenerative Medicine Project (described below in II. 2 (2))
 - Promoting academic-industrial collaboration in the development of automatic mass culture apparatus and peripheral devices ahead of the rest of the world and in projects focused on building manufacturing and quality control systems that are consistent with international standards.
 - The government will build a manufacturing system for ensuring the safe, cheap manufacture and processing of regenerative medicine products, etc., thereby encouraging the industrial application of iPS cells, etc. in regenerative medicine and increasing the international competitiveness of Japan's manufacturing industry in markets for the peripheral products underpinning regenerative medicine, such as culture apparatus.
 - Accelerating basic research, applied research, clinical research and trials, and practical applications for allogeneic cell transplantation therapies
 - By creating techniques for the high-efficiency establishment of uniform iPS cells, the government will build a safe iPS cell stock for use in regenerative medicine and promote the supply of iPS cells. Moreover, it will promote the development of stem cell manipulation technology and other research that will contribute to the practical application of allogeneic cell transplantation therapies.
 - As well as considering and preparing governmental and ministerial ordinances ahead of the entry into force of the Act to Ensure the Safety of Regenerative Medicine, etc., the government will provide support for clinical research and trials using human stem cells, and for research aimed at ensuring safety.
 - Building systems for conducting tests and inspections to ensure a high level of quality
 - The government will formulate evaluation criteria for clarifying the properties of iPS cells, and will establish and optimize iPS cell manufacturing and evaluation methods. It will also promote R&D focused on such areas as basic technologies that will assist in ensuring high levels of quality.

- The government will develop evaluation techniques for ensuring the quality and safety of iPS cells used as raw materials in regenerative medicine products, etc.

- Formulation and international standardization of drug evaluation techniques using iPS cell-derived differentiated cells

- The government will aim to establish safety evaluation techniques for next-generation drugs using human iPS cell technology. In addition, it will implement nationwide collaboration between industry, academia and government, focused on the development of standard cells and standard testing methods for evaluating cardiotoxicity, with a view to promoting their commercialization and proposing the international standardization of those evaluation techniques in FY2016.

- As well as responding to moves to establish standards within the International Organization for Standardization (ISO) and conducting studies and deliberations to examine whether or not the draft standards are suited to the actual situation within Japan, the government will participate in both Japanese and foreign ISO committees, conducting research aimed at the proposal of draft standards.

- Promoting collaboration between industry, academia and government that will assist in strengthening drug discovery research using iPS cells by developing technology for the establishment of disease-specific iPS cells, and for cell stock and analysis methods, as well as research into diseases and drug discovery research

- As well as establishing disease-specific iPS cells from the somatic cells of patients with various conditions and banking those cells, the government will aim to enhance the functions of banks at institutions serving as centers for research and clinical research in this field. It will also construct the infrastructure that will enable numerous researchers and companies to conduct drug discovery and other research.

- With the aim of conquering rare and intractable diseases, the government will promote research focused on identifying the etiology and pathophysiology of diseases using disease-specific iPS cells, and research aimed at developing therapies or preventive measures with a focus on drug discovery.

<Measures other than interministerial collaborative projects>

- Building infrastructure for gathering information about the post-approval effectiveness and safety of regenerative medicine products, etc.

- By FY2015, the PMDA will build a Regenerative Medicine Product Patient Record

System, which will serve as the basis for gathering information to ensure the post-approval effectiveness and safety of regenerative medicine products, etc.

- Formulating standards for raw materials used in regenerative medicine products, etc. and standards for clinical research and trials

- With a view to the entry into force of the Act to Partially Revise the Pharmaceutical Affairs Act (Act No. 84 of 2013) and the Act to Ensure the Safety of Regenerative Medicine, etc., the government will formulate standards concerning raw materials and other ingredients used in regenerative medicine products, etc. and the implementation of clinical research and trials.

(b) Bringing genomic medicine to fruition

Thanks to remarkable advances in genome analysis technology, the age is approaching when anyone can make use of their genomic information; indeed, genomic medicine – as typified by the selection of anticancer drugs and bone marrow transplant donors – has already begun. In Japan, biobank projects are being developed and success is being achieved in identifying the genes associated with certain diseases. Accordingly, the time is coming when specific measures should be formulated, to ensure that the results of genomic medical science become widely used in clinical settings. More specifically, it is necessary to build up information about genome polymorphism among Japanese (or East Asian) people and genomic information about enteric bacteria unique to Asian people, and to encourage R&D focused not only on the diagnosis and treatment of diseases, but also on the prevention of exacerbation and drug side-effects, and efforts to prevent onset in the first place. In addition, the environment for such R&D must be improved.

Accordingly, strengthening research infrastructure (biobanks, genome analysis, genome cohort studies) is vital; in developing this infrastructure, the need to gather and preserve high-quality biological specimens that are accompanied by detailed clinical information must be borne in mind. To utilize these clinical specimens in medical care and drug discovery, it is necessary to develop measurement techniques that can obtain the requisite data without fail and technologies that can analyze vast quantities of data, as well as providing supercomputers, and enhancing and managing the environment in terms of databases and other systems. In addition to the development of hard infrastructure, efforts to secure and cultivate experts in fields such as bioinformatics are required.

Furthermore, integrating multifaceted information is vital to efforts to shed light on

the mechanisms involved in the onset of disease via systematic studies of biomolecular networks and homeostatic mechanisms. Accordingly, it is necessary to develop centers for genome analysis, omics analysis, and image analysis, and to network these so that intensive analysis can be carried out. Moreover, R&D must be expedited further by enabling clinical specimens, clinical information, and information processing systems to be used externally, while ensuring that personal information is protected. Epigenomic studies concerning the interaction between environment and genes are also required.

With regard to personalized medicine, the development of companion diagnostics developed in tandem with therapeutic drugs must be promoted, as must efforts to optimize the design of clinical research and trials.

Personalized medicine based on genomic and epigenomic information or biomarkers is expected to become mainstream in medical care worldwide in the future. Collaboration between industry, academia and government is expected to yield progress in such areas as the development of simple, cheap, high-precision genetic diagnosis kits and new biomarkers. It is anticipated that the blending of information from special health check-ups with genomic information could be used for preventive measures aimed at extending the healthy life expectancy of the populace, as well as for clarifying the true nature of diseases.

As well as promoting genome research, consideration will be given to the handling of genomic information, including specific ethical responses and the need for legal restrictions, given the substantial impact that it will have on society in the future. Support will be required in relation to the ethical, legal and social implications of handling clinical information, as well as the fulfillment of various ethical guidelines. Collaboration with the patients, other citizens, communities and medical professionals offering their cooperation is also required.

International partnership and cooperation is vital when conducting initiatives in this realm. Strategic international cooperation that takes into account Japanese and global R&D trends, as well as the perspective of international competitiveness, will be required in pursuing partnerships with the U.S.A., which leads the world in terms of genome analysis technology and medical business, European countries such as the UK, Sweden, and Iceland, which have a substantial record of achievement with their large-scale cohorts, and neighboring countries in Asia, which have highly similar genomic information.

Accordingly, the government will implement the following measures.

<Interministerial collaborative projects>

- Japan Genomic Medicine Project (described below in II. 2. (2))

- Strengthening research infrastructure (biobanks, genome analysis, genome cohort studies)
 - As well as strengthening genome analysis functions and genome cohort studies by building biobanks of both those suffering from diseases and healthy individuals, the government will promote joint research focused on clinical applications.
 - To develop new therapies such as genomic medicine, the government will further enhance and strengthen the National Center Biobank Network (NCBN), which brings together specimens and clinical information from patients examined at National Centers. In addition, it will devote greater energies to promoting genome cohort studies that utilize this infrastructure.

- Enhancing the environment in relation to systems for utilizing clinical specimens in medical care and drug discovery
 - The government will devote greater efforts to promoting joint research with companies, etc. utilizing disease specimens held by the NCBN, in order to further promote the development of therapeutic drugs by companies and other research institutes. In addition, it will make environmental improvements to systems as needed, to make them easier for companies and others to utilize, including further enhancing the NCBN's catalog database.

- Deliberations on enabling clinical specimens, clinical information, and information processing systems to be used externally in a way that protects personal information
 - The government will encourage organic partnerships to enable organizations conducting research aimed at bringing genomic medicine to fruition to use the specimens and clinical information held at each biobank. Such organizations will be provided with the material and information in question once the necessary screening procedures have been completed in relation to the handling of personal information and the quality of their research.

- Support for fulfilling various ethical guidelines
 - The government will promote research focused on resolving specific issues, including the inevitable ethical, legal and social implications arising from efforts to translate

genomic medicine into reality. As such, by FY2016, it will make recommendations that will assist in the reflection of these matters in the Ethical Guidelines for Human Genome/Gene Analysis Research.

- Promoting strategic international cooperation

- In response to moves within the International Organization for Standardization (ISO) to establish a standard for biobanks, the government will undertake studies and deliberations to examine whether or not the draft standard is suited to the actual situation within Japan. In addition, it will conduct research aimed at proposing draft standards tailored to the actual situation in Japan to both Japanese and foreign ISO committees, as needed.

- With a view to working in partnership with genomic medicine research institutes in other countries, the government will formulate a strategy for the protection of intellectual property acquired from genomic medicine research, aiming to obtain recommendations on practice by FY2016.

- The government will participate in international cooperative frameworks focused on the cancer genome and genomic medicine, as well as frameworks in these fields within ISO.

- Promoting simultaneous development of companion diagnostics in personalized medicine, etc. and optimizing the design of clinical research and trials (described above: II. 1. (5) (b))

<Measures other than interministerial collaborative projects>

- Promoting research concerning genome analysis, etc.

The government will promote R&D concerning genome analysis, etc. at RIKEN, the national centers for advanced and specialized medicine, and the National Institute of Advanced Industrial Science and Technology.

- Promoting international research exchange and cooperation concerning genomic medicine

- In the field of genomic medicine, the government will promote international research exchange and cooperation between government departments, researchers, and organizations.

(c) Other initiatives focused on advanced R&D

With the advanced science and technology at its disposal, Japan needs to make progress not only in the aforementioned areas of (a) bringing regenerative medicine to fruition, and (b) bringing genomic medicine to fruition, but also in identifying the pathophysiology of other diseases. In addition, proactive initiatives are required in the cultivation of groundbreaking new seeds with great potential to become the drugs, medical devices, and medical technology of the future, including the development of new therapies based on this research, such as gene therapies, virotherapy, immunotherapy, vaccine therapy, molecular-targeted therapy, and nucleic acid medicine, as well as the development of DDS and innovative drugs and medical devices that will assist in high-precision, highly safe diagnosis and treatment. Proactive initiatives are also required in regard to biopharmaceuticals, the market for which is expected to expand substantially in future.

Moreover, particular efforts must be made to strengthen and promote the development of next-generation technologies, instruments, and systems for measurement, analysis, and evaluation, which will provide powerful support to the world's most advanced R&D in the field of medical science and medical care, as well as the clinical application thereof. This is an urgent task, as it is essential to efforts to achieve the world's most advanced medical care, as well as to the elimination of Japan's annual trade deficit of 2 trillion yen.

Accordingly, the government will implement the following measures.

- Cultivating groundbreaking new seeds
 - Based on R&D targets established on objective evidence, the government will promote the world's most advanced R&D aimed at the creation and cultivation of groundbreaking seeds, and will accelerate and promote in-depth research focused on the most promising results, in order to create innovative drugs, medical devices, etc. and medical technology.
 - Making use of the potential cultivated through the substantial volumes of research conducted to date at RIKEN and other research and development corporations, the government will conduct basic research that will contribute to the creation of innovative seeds.

- Promoting proactive initiatives in regard to biopharmaceuticals, the market for which is expected to expand substantially in future

- With a view to strengthening the international competitiveness of Japan's biopharmaceuticals, the government will work on integrating chemical biology and computational chemistry, which are Japan's strengths, and will develop the world's first basic technology for the creation of biopharmaceuticals, including technology focused on subcellular targets and efforts to improve the functions of nucleic acid medicine. In doing so, it will aim to transfer this technology to companies within five years.

- In 2015, the government will begin considering support for the development of infrastructure and environmental improvements, including human resource development, aimed at the creation of innovative biopharmaceuticals originating in Japan.

- To translate next-generation treatment and diagnosis into reality, the government will develop technologies for searching biomarkers, to facilitate early diagnosis without imposing a burden on patients, as well as the IT required for next-generation drug discovery, technology for developing natural compound libraries, and high-quality biopharmaceutical manufacturing technology, aiming for the practical application of these within five years.

- Encouraging the development of next-generation technologies, instruments, and systems for measurement, analysis, and evaluation

- The government will promote the development of diagnostic technologies, instruments, and systems that will contribute to the provision of low-cost medical diagnosis that minimizes the burden on the patient, and of technologies, instruments, and systems for measurement and analysis that will facilitate efforts to explore unknown targets.

(6) Initiatives based on international perspectives

(a) Setting themes with an international perspective

In setting R&D themes and considering initiatives, it is essential to gain a precise grasp of the current state of R&D not only within Japan, but also overseas, as well as clarifying international trends in industrial competitiveness and the status of international standardization. Accordingly, when setting themes, adequate consideration is required from an international perspective as well, so it is necessary to cultivate and utilize not only experts in individual fields, but also personnel with an international outlook. Moreover, when selecting topics, it is necessary to ensure an adequate hearing for the opinions of both Japanese and foreign scientists in the relevant specialist discipline.

(b) International cooperation and expansion, and efforts to make an international contribution

It goes without saying that international collaborative research in the field of medicine is vital. Cooperation with Western and other countries conducting advanced R&D in the world's most advanced fields is important in genome research and the development of next-generation diagnostic and therapeutic techniques. In particular, in the case of genome research, collaboration with other Asian countries is essential, given the high degree of similarity at the genetic level. Moreover, promoting international cooperation is also essential to improve the precision of data from patients with intractable diseases, lifestyle-related diseases, and other conditions, enabling such data to be utilized effectively. Support systems for conducting international collaborative research must also be strengthened, including the development of high-quality clinical research and trials, and the establishment of research networks.

The globalization of transport and logistics in recent years has made international collaboration essential in efforts to combat infectious disease. In particular, bilateral and multilateral cooperation that includes Asian and African countries is required, with international partnerships being utilized to provide diverse cooperative responses in such areas as early detection, containment, and drug discovery. At the same time, tuberculosis, drug-resistant bacteria, and other infectious diseases are still a major problem in developing countries, so there is great international need for vaccines and diagnostic and therapeutic drugs targeting infectious diseases. Accordingly, Japan must encourage technological innovation to make an international contribution in this area. Making an international contribution and engaging in international cooperation in this way is vital for R&D in Japan as well, and will ultimately lead to the achievement of sustainable development worldwide.

Based on the perspective of industrialization, core technologies in the field of diagnostic imaging have been created through strong partnerships with medical institutions, resulting in the development of advanced drugs, medical devices, etc. and medical technology. The government will further strengthen these, thereby accelerating efforts to contribute to medical care and expand overseas. In addition, Japan's industrial competitiveness must be strengthened through cooperation in the provision of medical services and development of systems suited to the circumstances and needs of counterpart countries in Asia and Africa, among others, while demonstrating an awareness of sustainable business development that truly contributes to medical care in the counterpart country.

Furthermore, positioning global health as a key issue in Japanese diplomacy, there is

a need to mobilize knowledge from throughout Japan in order to ensure that everyone around the world can enjoy basic medical care services at an affordable price (universal health coverage).

Accordingly, the government will implement the following measures.

- Cooperation in the provision of medical services and the development of systems suited to the circumstances and needs of the counterpart country
 - The government will establish a wide range of cooperative relationships to serve as infrastructure for conducting projects, thereby facilitating activities by Japanese medical personnel within the counterpart country. Efforts in this area will include coordination in the area of health care systems, recommending local adoption of standards relating to drugs, medical devices, etc. and medical technology, including Japanese diagnostic criteria, support for the introduction of insurance systems, and assistance in constructing the public finance schemes required for the establishment and running of medical institutions.
 - The government will promote the ASEAN Health Initiative to transform the countries of ASEAN into advanced nations in terms of achieving a healthy life expectancy. To this end, Japan will transfer the experience and knowledge that it has gained as a pioneer in such areas as promoting healthy lifestyles, early detection, and preventive medicine, as well as support for the construction of public medical insurance systems.

- Accelerating overseas expansion in fields including diagnostic imaging
 - The government will build Japanese-style medical centers, primarily in emerging economies, to promote the overseas expansion of Japan's drugs, medical devices, etc., medical technology, and medical services, including in the field of diagnostic imaging, which is one of the country's strengths.

- Promoting international research exchange and cooperation concerning genomic medicine (described above: II. 1. (5) (b))

- Promoting R&D in the world's most advanced fields and international collaborative research focused on resolving global issues
 - As well as conducting R&D focused on advanced medical care, the government will promote joint research with advanced countries, emerging economies, and developing countries via strategic international science and technology cooperation, to contribute to

the resolution of global issues affecting medical care.

(c) International harmonization of regulations, etc.

The importance of international standards is growing as the global economy becomes increasingly borderless. To facilitate the entry of Japanese drugs and medical devices, etc. to markets across the globe, it is necessary to ensure international harmonization of regulations and to be proactive in strengthening the development of personnel and systems involved with international regulatory affairs.

Moreover, the promotion of strategic international standardization initiatives focused on proposing international standards on safety, etc. in areas where Japan has outstanding technologies, such as advanced medical devices and regenerative medicine technologies, is vital in order to bolster Japan's international competitiveness.

Accordingly, the government will implement the following measures.

- Strengthening the development of personnel and systems involved with international regulatory affairs

- The government will strengthen collaboration by the PMDA with the FDA in the U.S.A., the EMA (European Medicines Agency) in Europe, and other international organizations in the West and Asia, promoting the exchange of information about reviews and consultations, including more active exchanges of information about GCP surveys, etc. In addition, to cultivate personnel capable of playing an active role internationally, it will promote people-to-people exchange and attendance at ICH and other international conferences examining international guidelines.

- Promoting strategic international standardization initiatives

- The government will promote international standardization by enhancing research concerning evaluation of the effectiveness and safety of drugs and medical devices, etc. that utilizes cutting-edge technology. It will also offer pioneering proposals for the formulation of international standards and criteria concerning state-of-the-art diagnostic and therapeutic techniques. Through this, by 2020, the government will aim to formulate international standards proposed by Japan.

(7) Human Resource Development

Securing and cultivating personnel in all relevant fields is vital to efforts to improve medical R&D potential.

Universities also have a key role to play in human resource development from the perspective of clinical research and trials. In particular, it is expected that they will provide students with education concerning clinical research and trials, incorporating methodologies, clinical epidemiology, and biostatistics relating to such research and trials into undergraduate education. Moreover, it is vital to provide ongoing support for young researchers in the fields of medicine and the life sciences, in order to cultivate personnel who are well-versed in everything from basic research to clinical research and trials, have a record of world-class academic achievements, and can demonstrate strong leadership.

Furthermore, it will promote initiatives aimed at improving the mobility of researchers and other personnel. Improving understanding (literacy) concerning health and disease is a crucial issue, not only among experts, but also among the wider population.

In addition, it is necessary not only to nurture researchers capable of becoming leaders, but also to secure, cultivate, and provide appropriate evaluation for the requisite specialist personnel, specifically biostatisticians, CRCs (clinical research coordinators), data managers, and specialists in the fields of intellectual property, the evaluation of effectiveness and safety, regulation, ethics, and public relations, as well as experts in regulatory science. Career paths must be established for such personnel. Consideration must be given to deploying multiple personnel of this nature at translational research support centers, core hospitals for clinical research, and centers for early and exploratory clinical trials.

Moreover, it is vital to cultivate personnel capable of conducting multidisciplinary research and creating innovation, to ensure that innovative drugs, medical devices, etc. and medical technology reach clinical research sooner.

Accordingly, the government will implement the following measures.

- Ongoing support for young researchers in the fields of medicine and the life sciences
 - Encouraging young researchers to participate in advanced R&D will support challenging research that gives full play to their creativity and ingenuity, thereby helping to foster researchers who will become the next generation of leaders.

- Securing and cultivating specialist personnel and experts in regulatory science
 - At translational research support centers, the government will promote efforts to secure specialist personnel, including data managers, biostatisticians, cell culture

technicians, and experts in regulatory science, as well as promoting human resource development via education, training courses, and OJT.

- To nurture support staff for clinical research and trials, so that high-quality clinical research and trials can be implemented, training for entry-level clinical research coordinators (CRCs), senior CRCs, and data managers (DMs) will continue, along with training for ethical review board members, with the aim of cultivating more than 500 senior CRCs by FY2016. In addition, the government will aim to launch in FY2015 (i) training for physicians involved in clinical research and trials, and (ii) efforts to coordinate the eligibility requirements for examinations targeting senior CRCs certified in the private sector, as well as the content of those examinations. (Described above: II.

1. (1) (a))

- Cultivating innovative personnel

- To cultivate innovative personnel, the government will actively promote the introduction of advanced programs and people-to-people exchange at translational research support centers.

(8) Fair research mechanisms and improving the environment to ensure ethical, legislative, and regulatory compliance

To develop fair research mechanisms, it is necessary to build databases to facilitate efficient clinical research and trials. In addition, clinical research audits and monitoring must be established. More specifically, efficient implementation of R&D management is required, including the formulation of research protocols, updates on the progress of research, management of research data (data input, collation, and analysis), and management of research results and intellectual property.

As well as making steady progress with the revision of the Ethical Guidelines for Clinical Studies, which are currently under review, it is necessary to improve the quality of ethics committees by introducing an accreditation system for ethical review boards. Moreover, in parallel with the review of ethical guidelines, the government will aim to undertake deliberations in the autumn of 2014 regarding systems relating to clinical research, including the legal system. In doing so, the government will strengthen ethics education, publicize cases of fraud, improve the environment for fraud prevention, establish systems that impose liability on the organization as a whole, pursue managerial liability for cases of fraud, strengthen and enhance the government's monitoring functions, and promote government initiatives to prevent fraud at organizations, with the objective of ensuring the quality of clinical research, protecting

test subjects, and managing conflicts of interest on the part of research institutes and pharmaceutical companies.

To promote initiatives to prevent irregularities in basic and clinical research, AMED will, throughout its duties, strive to accumulate know-how concerning responses to irregularities in medical R&D and to cultivate personnel specializing in this area.

Accordingly, the government will implement the following measures.

- Dealing with research-related fraud

- While giving adequate consideration to the reality of frontline research, the government will examine research fraud from the broader perspective, looking beyond individual cases, and will compile a list of the responses required by researchers, organizations involved in prevention, and organizations involved in dealing with fraud after it has occurred. In addition, it will notify the relevant ministries of its findings and promote initiatives in this area.

- The government will ensure thorough awareness of the content of any revisions to guidelines on malpractice and the management and auditing of public research funds at research institutes, and will promote initiatives aimed at ensuring compliance with these.

- With a view to restoring trust in Japanese clinical research, the government will move forward with the review of the Ethical Guidelines for Clinical Studies, taking into account the report by the Investigative Committee on the Incident Involving Clinical Research into an Antihypertensive Drug, and will aim to begin considering approaches to systems related to clinical research, including the legal system, by the autumn of 2014.

- Introducing an accreditation system for ethical review boards

- In light of the increasingly advanced, complex situation arising from the growing need to conduct clinical research at an international level, the role played by ethical review boards in making appropriate judgments on the ethical and scientific justification for research is becoming even more important. In FY2014, a system for the accreditation of ethical review boards that meet standards prescribed by the government will be introduced, targeting the country's 1,300 or so ethical review boards. As well as ensuring the quality of reviews conducted by these ethical review boards, overall improvements in their quality will be sought.

(9) Developing the research base

Providing ongoing, solid support for basic technology that will lead to drug discovery and the development of medical device is essential. In addition, innovation must be created through the integration of a variety of specialist fields. Accordingly, it is necessary to build an integrated system for translating the fruits of groundbreaking basic research in academia into practical applications, by bringing together centers promoting such efforts as part of the Project for Japan Translational and Clinical Research Core Centers.

Furthermore, R&D starts with the sharing of knowledge, so efforts must be made to ensure that high-quality information and samples are gathered, stored, and shared as widely as possible, including life science databases, nationwide databases of intractable diseases, and big data database systems. It is essential that the databases built up by individual ministries also be part of such collaboration. In addition, appropriate targets must be set to ensure that grassroots research into diseases and epidemiological studies are not neglected, and the stable maintenance of R&D requiring long-term support must be considered.

Furthermore, it is vital to promote the development of the research base (samples from patients, bioresources from animal models, advanced analytical techniques and instruments, etc.) and make the latest infrastructure (live molecular imaging, next-generation sequencers, etc.) available to researchers. In addition, common science and technology infrastructure must be made more accessible through partnerships with existing large-scale advanced research infrastructure (synchrotron radiation facilities, supercomputers, etc.) and small-scale facilities with cutting-edge measurement and analysis instruments, so that it can be used to further promote medical R&D.

All possible measures will be taken to ensure the smooth transition of duties relating to support for drug discovery from the National Institute of Biomedical Innovation to AMED, particularly the transfer of its functions as the headquarters of the Drug Discovery Support Network. Furthermore, the government will build a network consisting of universities, research and development corporations, and other research institutes and companies, to promote the development of medical device.

Accordingly, the government will implement the following measures (see II. 1. (4) for ICT initiatives)

- Developing infrastructure for research in the life sciences, etc.
- To integrate databases concerning research in the life sciences, the government will

promote R&D focused on data integration and search techniques and will put in place cross-cutting information infrastructure.

- The government will support research at universities, etc. by building advanced, shared drug discovery and medical technology support infrastructure, including technologies and facilities that will assist in drug discovery and other life science research.

- With a view to advancing research in the life sciences, the government will strategically collect and store important, high-quality bioresources at key centers, and will make these available to research institutes.

- As well as strengthening genome analysis functions and genome cohort studies by building biobanks of both those suffering from diseases and healthy individuals, the government will promote joint research focused on clinical applications.

- The government will promote efforts to upgrade and share the advanced research facilities and equipment of universities and incorporated administrative agencies, as well as promoting the development of common basic technology.

- Making full use of the innovative High Performance Computing Infrastructure (HPCI) centered on the “K computer” supercomputer, the government will establish simulation techniques for medical care and drug discovery, thereby further promoting more advanced medical care and drug discovery processes.

- To bring genomic medicine to fruition and develop new therapies, the government will further enhance and strengthen the National Center Biobank Network (NCBN), which brings together specimens and clinical information from patients examined at National Centers.

(10) Intellectual property management initiatives

In seeking to increase Japan’s international competitiveness in the field of medical care, the government will promote strategic IP initiatives, such as enhancing IP education, and cultivating and utilizing experts in IP.

Moreover, from the perspective of the initiatives required for drug repositioning, it is necessary to ascertain the status of intellectual property and enhance the environment to facilitate the provision of information by pharmaceutical companies.

- To deal with such issues, a dedicated department will be established in AMED to provide support functions for research institutes, with a view to the acquisition of intellectual property (intellectual property management and advice desk, support for the formulation of intellectual property acquisition strategies, etc.)

Accordingly, the government will implement the following measures.

- Initiatives under the Project for Japan Translational and Clinical Research Core Centers
 - The government will further promote specialized support for patent applications and patent search, intellectual property management, and intellectual property strategy formulation in the field of medicine, by ensuring that translational research support centers have access to patent attorneys and other intellectual property experts. Moreover, the government will promote education and on-the-job training concerning translational research, including intellectual property education, targeting both undergraduate and graduate students.

- Initiatives under the Program for Strategic Development of Anti-Cancer Research Seeds in Next Generation
 - The government will deploy intellectual property experts to formulate patent application strategies after conducting prior art searches concerning research seeds, which would be difficult for individual research institutes to carry out alone, as well as conducting competing technology surveys and market research. In addition, it will undertake technology transfer and licensing out to companies, followed by powerful support through the practical application stage.

- AMED initiatives (described below in II. 2. (1))

2. The Role that the New Medical R&D System Should Play

In May this year, the Act on Promotion of Healthcare Policy and the Act on the Independent Administrative Agency of Japan Agency for Medical Research and Development were enacted, establishing AMED and putting in place a new system for medical R&D in Japan.

More specifically, the Headquarters for Healthcare Policy was established within the Cabinet (with the Prime Minister as Director-General and all other Cabinet ministers as members) to provide control tower functions focused on medical R&D. Under their political leadership, the Headquarters is tasked with (1) formulating the Healthcare Policy, to serve as the guidelines for comprehensive, long-term measures that the government should take in regard to advanced R&D and the creation of new industries in the field of healthcare and medical care, as well as formulating the Plan for Promotion of Medical Research and Development in accordance with this policy; (2)

securing the budget required for control tower functions and allocating budgets in a strategic, selective manner by consolidating the medical R&D budgets allocated to each ministry for implementing this policy and plan; and (3) ensuring the appropriate allocation to AMED of program directors (hereinafter “PDs”) and program officers (hereinafter “POs”) with abundant experience in basic research, clinical research and trials, and drug discovery and development, thereby ensuring seamless, integrated management of research focused on practical applications from the basic research stage onward.

The following specific initiatives will be implemented under this new system for medical R&D.

(1) AMED’s expected functions

(a) Management of medical R&D

The success or failure of interministerial collaborative projects and other R&D implemented by AMED is dependent upon project management. Accordingly, it will conduct management in such a way as to ensure that plans are constantly reviewed on the basis of a realistic vision, identifying the needs of patients, clinical research , and industry, and evaluating technical potential. To this end, it must be equipped with the capacity to spot outstanding seeds, planning ability that will facilitate translation into clinical research and trials and licensing out to industry, and the power to drive meticulous preparation for regulatory compliance and the provision of support and guidance to researchers.

More specifically, as well as an advisory board reporting to the President of AMED, to identify the needs of patients, clinical research , researchers, and industry, it will be equipped with experts who can provide think-tank functions, pinpointing themes by identifying and evaluating trends within Japan and overseas. Moreover, a peer review system will be introduced for the selection of individual research topics. PDs and POs must use this to ensure seamless, integrated project management functions throughout the R&D process, from the commencement of R&D through its promotion, monitoring and management, and on to any change in policy. This includes the implementation of research based on the Expert Panel’s report, the identification and investigation of research trends, the strengthening of research aimed at exploring and cultivating seeds (screening and optimization research), integrated management that links outstanding basic research results into clinical research and trials and on to commercialization (progress management and advice on research, regulatory compliance, etc.), and monitoring and management functions to ensure the appropriate conduct of research.

To promote initiatives to prevent irregularities in basic and clinical research, AMED must, throughout its duties, strive to accumulate know-how concerning responses to irregularities in medical R&D and to cultivate personnel specializing in this area.

(b) Data management in clinical research and trials

AMED must consider measures for efficiently managing the research that it promotes, including the formulation of clinical research and trial protocols, updates on the progress of research, management of research data (data input, collation, and analysis), and management of research results and intellectual property. It must also conduct initiatives to ensure that these are implemented as soon as possible.

(c) Support for practical applications

AMED must be equipped with support functions aimed at assisting research institutes in the acquisition of intellectual property; these functions include an intellectual property management and consultation service and support for the formulation of intellectual property acquisition strategies. In addition, it must be able to support collaboration with companies focused on practical application, offering assistance and advice concerning the formulation of exit strategies for promising seeds (in partnership with the PMDA), providing information and matching services to companies, and ensuring a one-stop service. AMED must build networks that enable support for the development of medical device to be provided through partnerships among relevant bodies. Collaboration between medicine and industry and academic-industrial collaboration will play a core role in this, so AMED needs to enhance its functions as a hub for such collaboration.

In terms of support for the practical application of drugs, it must provide powerful nationwide support for the creation of innovative new drugs, with a primary focus on the application stage (screening, optimization research, and nonclinical tests). This should be achieved through the evaluation of research results from universities, etc. by a team of drug discovery support coordinators, who will select promising seeds from among them so that the drug discovery support resources of the Drug Discovery Support Network can be intensively channeled toward those seeds.

(d) Support for the development of R&D infrastructure

AMED must develop systems for the seamless development of innovative diagnostic techniques and instruments through the exploration and identification of new biomarkers, and diagnostic techniques and instruments that make known biomarkers

easier to handle and are capable of accurately and cheaply measuring them in a non-invasive or minimally-invasive way. In addition, it must strengthen the Innovative Medical Technology Creation Centers and enhance their systems, enhance biobanks for developing preventive medical care and service techniques based on evidence, and make animal models and other bioresources available.

(e) Promoting international strategies

As well as promoting international collaborative research that is truly valuable to Japan, taking into account international trends in R&D, Japan's research capabilities in the field of medicine must be utilized to make a contribution on the international stage.

Accordingly, the government will aim to establish AMED on April 1, 2015 and equip it with the necessary functions.

(2) Implementing projects with an integrated path from basic research through to practical application

This Plan aims to identify outstanding seeds among the fruits of basic research and to create a seamless path through to their practical application, with a view to yielding concrete results. Accordingly, the initiatives must, from their very outset, be implemented on the basis of a strategy for translation into clinical research and trials and licensing out to industry, along with meticulous preparations for this.

Of the wide-ranging medical R&D initiatives, the initiatives approved by the Headquarters for Healthcare Policy on August 30, 2014 as interministerial collaborative projects to be launched in FY2014 will be run in an integrated manner as a single project, bringing together the relevant R&D programs of each ministry. These will be managed by AMED in an integrated fashion after its establishment, but until then, the administrative departments of each ministry will work together, putting in place joint committees and other systems for the integrated promotion of the programs in which each ministry is involved. KPIs are set for individual projects and PDs will be granted authority and discretion concerning such matters as the launch of individual R&D projects and any changes of policy, with a view to the achievement of these KPIs. It is envisaged that the research teams working under each PD will search for and select seeds with a focus on the exit point, conduct R&D based on the strategy for each individual seed, and select alternative new seeds as needed, in the event of a setback with a particular seed. Through this, a management system will be established that ensures that R&D of multiple seeds is being carried out by each team at all times. In

addition, the following KPIs have been set for the interministerial collaborative projects in question, and initiatives will be implemented on the basis of these KPIs. These KPIs will be examined and verified further, depending on the situation, and may be revised if necessary. KPIs will also be set for any interministerial collaborative projects launched in the future.

Initiatives other than the interministerial collaborative projects will be steadily promoted, taking into account the goals of this Plan.

It is anticipated that support will be offered for topics that are risky, but have substantial potential, with a view to achieving groundbreaking innovation.

In promoting these interministerial collaborative projects, efforts will be made to enhance management and regulatory science, and allocate resources in such a way as to ensure that they respond nimbly to sudden progress in research and groundbreaking advances in relevant areas of science and technology, while also advancing basic research into diseases.

○ Drug discovery

The government will enhance infrastructure to support drug discovery, such as the Drug Discovery Support Network, and promote seamless support from the basic research stage through to practical application as a drug. The KPIs and interministerial collaborative projects are as follows.

[KPIs to be achieved by FY2015]

- Consulting and evaluation of seeds: 400 cases
- Drug discovery support for promising seeds: 40 cases
- Licensing-out to companies: 1 case

[KPIs to be achieved by around 2020]

- Consulting and evaluation of seeds: 1,500 cases
- Drug discovery support for promising seeds: 200 cases
- Licensing-out to companies: 5 cases
- Identification of drug discovery targets: 10 cases

● Project for Drug Discovery and Development

- Through the establishment of the Drug Discovery Support Network, the government will support R&D focused on new drug discovery and strengthen infrastructure for supporting drug discovery, working in partnership with universities and industry. Moreover, it will promote research aimed at identifying drug discovery targets, technology development that will form the basis for drug discovery, and research

relating to the practical application of medical technology, thereby supporting the development of innovative drugs and drugs to treat rare diseases.

○ Development of medical device

The government will promote the development and practical application of outstanding medical device originating in Japan, giving thorough consideration to medical needs and utilizing the manufacturing technology in which Japan excels. In addition, it will enhance systems for linking R&D into practical applications. The KPIs and interministerial collaborative projects are as follows.

[KPIs to be achieved by FY2015]

- Formulate 10 new guidelines for promoting the development and practical application of medical device
- Expand the scale of the domestic market for medical device (from ¥2.4 trillion in 2011 to ¥2.7 trillion)

[KPIs to be achieved by around 2020]

- Double the value of medical device exports (from approx. ¥500 billion in 2011 to approx. ¥1 trillion)
- Put at least 5 types of innovative medical devices to practical application
- Expand the scale of the domestic market for medical device to ¥3.2 trillion

● Project for Medical Device Development

- To encourage the development of medical device via collaboration between medicine and industry, the government will establish a system to enable multiple specialist support organizations to support the development of such device (the Medical device Development Support Network (tentative name)), and will utilize Japan's advanced technical abilities in conducting R&D focused on creating technological seeds and linking these into the practical application of medical devices and systems. Moreover, it will conduct initiatives aimed at expediting the process of reviews for the approval of medical device and will cultivate R&D personnel.

○ Innovative Medical Technology Creation Centers

As well as building an integrated system for translating the fruits of groundbreaking basic research in academia into practical applications, the government will develop systems for implementing and supporting high-quality world-class clinical research and trials focused on seeds at each development stage. The KPIs and interministerial collaborative projects are as follows.

[KPIs to be achieved by FY2015]

- Number of physician-led clinical trials notified: 21 per year
- First in Human (FIH) studies (including company-initiated clinical trials): 26 per year

[KPIs to be achieved by around 2020]

- Number of physician-led clinical trials notified: 40 per year
- FIH studies (including company-initiated clinical trials): 40 per year

- Project for Japan Translational and Clinical Research Core Centers

- To build an integrated system for translating the fruits of groundbreaking basic research in academia into practical applications, the government will use this project to further the integration of translational research support centers, centers for early and exploratory clinical trials, core hospitals for clinical research, and centers for Japan-led global clinical research. In addition, it will further endeavor to strengthen the functions of these centers and make them more distinctive, including through the securing and cultivation of personnel, as well as developing networks, promoting open access, and expanding the range of seeds.

- It will also develop these centers as facilities with ARO functions, providing support for multi-institutional joint research, as well as conducting high-quality world-class clinical research and trials that comply with ICH-GCP, and physician-led clinical trials.

- Regenerative medicine

As well as providing seamless, integrated support from the basic stage through to the clinical phase, the government will enhance infrastructure for projects focused on regenerative medicine and provide support aimed at the utilization of iPS cells, etc. as tools to assist in drug discovery, thereby increasing the efficiency of new drug development. The KPIs and interministerial collaborative projects are as follows.

[KPIs to be achieved by FY2015]

- Number of research projects using human stem cells, etc. that have transitioned into clinical research or clinical trials: approx. 10 projects

(E.g. age-related macular degeneration, corneal disease, injuries to the meniscus of the knee, bone and cartilage reconstruction, blood disorders)

- Develop drug discovery technology using iPS cells

[KPIs to be achieved by around 2020]

- Develop clinical applications for new therapeutic drugs manufactured using iPS cell technology

- Increase the number of pharmaceutical approvals granted for regenerative medicine

products, etc.

- Expand the scope of target diseases that transition into the clinical research or trial stage: approx. 15 cases⁶

- Put peripheral equipment and apparatus related to regenerative medicine into practical application

- Present a proposal for international standardization of a method for evaluating drug cardiotoxicity using iPS cell technology

- Japan Regenerative Medicine Project

- With a view to ensuring that regenerative medicine using iPS cells, etc. becomes a reality without delay, the government will undertake initiatives aimed at achieving a safe supply of iPS cells, develop and share stem cell manipulation technologies and other technologies that will assist in the practical application of iPS cells, and promote basic research and nonclinical tests in the field of regenerative medicine. In addition, it will promote clinical research and trials focused on regenerative medicine and develop safety evaluation techniques for regenerative medicine products, etc. Furthermore, the government will establish industrial infrastructure to underpin efforts to bring regenerative medicine to fruition.

To improve the efficiency of new drug development, it will form partnerships to support research in such areas as drug discovery using iPS cells, etc. Moreover, the government will present a proposal for the development and international standardization of a method for evaluating cardiotoxicity using iPS cell technology. Furthermore, it will establish industrial infrastructure to underpin efforts to provide support for drug discovery using stem cells.

- Genomic personalized medicine

In light of the rapid pace of progress in technology for genome-level analysis, the government will seek to strengthen the infrastructure for such analysis, to feed back to the public the results of efforts to clarify the relationship between disease, genetic factors, and environmental factors. In addition, it will promote efforts to shed greater light on specific diseases, as well as promoting the clinical application of the results. The KPIs and interministerial collaborative projects are as follows.

[KPIs to be achieved by FY2015]

- Establish collaboration between such bodies as BioBank Japan, the National Center Biobank Network, and Tohoku Medical Megabank

⁶ Including around 10 cases with FY2015 as the target.

- Establish full genome and diversity databases concerning diseases
- Identify the standard genome sequence for Japanese people and genes that predict prognosis in various diseases

- Establish predictive diagnostics for side-effects from anticonvulsants

[KPIs to be achieved by around 2020-30]

- Dramatically improve therapies for lifestyle-related diseases (diabetes, stroke, myocardial infarction, etc.)

- Establish predictive diagnosis of cancer incidence, and of reactions to and adverse side-effects from anticancer drugs

- Start clinical research concerning genome therapy for depression and dementia

- Develop innovative methods of diagnosing and treating incurable neuromuscular diseases

- Japan Genomic Medicine Project

- As well as building biobanks of both those suffering from diseases and healthy individuals, the government will conduct data analysis of information from genome analysis and clinical information in order to identify and verify the causes of the onset of disease and the genes affecting drug response. In addition, it will work on identifying the standard gene sequence for Japanese people. Moreover, through the implementation of joint research and additional genome studies, the government will seek to identify the genes that cause intractable and rare diseases, among others, as well as promoting research that will assist in the formulation of guidelines for innovative diagnostics and treatments utilizing genomic information. Furthermore, it will promote experimental and empirical clinical research aimed at enhancing the research base with a view to making genomic medicine a reality, and establishing systems for the provision of genomic medicine.

- Disease-specific research

<Cancer>

Based on the 10-Year Strategy for Cancer Research (approved by the three relevant Cabinet ministers in March 2014), which was formulated in accordance with the Basic Plan to Promote Cancer Control Programs (approved by the Cabinet in June 2012), the government will follow an integrated approach in promoting everything from basic research aimed at shedding light on the true nature of cancer to research focused on practical applications, working in partnership with the research projects being overseen by relevant ministries. The KPIs and interministerial collaborative projects are as

follows.

[KPIs to be achieved by FY2015]

- Acquire 10 promising seeds for new anticancer drugs
- Acquire 5 biomarkers for early diagnosis and predictive markers for immunotherapy
- Reduce death rates due to cancer by 20% (reduce the age-adjusted death rate among those aged under 75 by 20% from the 2005 level by 2015)

[KPIs to be achieved by around 2020]

- License out at least 10 types of drug for clinical trial within 5 years, with a view to developing innovative anticancer drugs based on Japanese technology
- License out at least 6 types of drug for clinical trial, with a view to establishing practical applications for therapeutic drugs to treat pediatric, refractory, and rare cancers, including unapproved and off-label drugs
- Obtain approval or additional indications for at least 1 type of drug to treat pediatric and rare cancers, etc.
- Eliminate the so-called drug lag and device lag
- Establish standards of care for cancers that affect pediatric and elderly patients, and for rare cancers (formulate at least 3 sets of guidelines)

● Japan Cancer Research Project

- Carefully selecting promising results from basic research, the government will promote research aimed at the development of drugs and medical devices with a view to their practical application, and will license the results out for clinical research and trials. In addition, it will feed clinical data from clinical research and trials back into basic research, to expedite the development of practical applications for use in treating cancer, including the development of drugs and medical devices.

<Neuropsychiatric disorders>

The government will establish innovative diagnostic, preventive, and therapeutic techniques to conquer dementia and psychiatric disorders, by devoting substantial efforts to R&D and infrastructure development based on collaboration between the relevant ministries, with a view to identifying the neural circuits and functions in the brain associated with the onset of dementia, as well as depression and other psychiatric disorders. The KPIs and interministerial collaborative projects are as follows.

[KPIs to be achieved by FY2015]

- Establish very early diagnosis methods for dementia, using molecular imaging
- Discover at least one new biomarker for the diagnosis of psychiatric disorders,

response to drug therapy, and side-effects, and complete clinical evaluation for the identification process

[KPIs to be achieved by around 2020]

- Start clinical trials of drug candidates originating in Japan for radical treatment of dementia, depression, and other psychiatric disorders
- Establish objective diagnostic techniques for psychiatric disorders
- Establish appropriate drug therapies for psychiatric disorders
- Complete maps of the structure and activity of all neural circuits in the brain

● Project for Psychiatric and Neurological Disorders

- As well as promoting R&D and infrastructure development aimed at identifying the structures and functions of neural circuits throughout the brain and developing biomarkers, the government will aim to shed light on the onset mechanism of dementia, depression, and other psychiatric disorders, and establish diagnostic techniques and appropriate therapies for these.

<Emerging and re-emerging infectious diseases>

To protect both Japanese citizens and people worldwide from new forms of influenza and other infectious diseases, the government will strengthen measures to combat infectious diseases by promoting research at home and overseas into infectious diseases, based on collaboration between the various ministries, and will ensure more efficient, effective linkage of these results into the development of therapeutic drugs, diagnostic drugs, and vaccines. The KPIs and interministerial collaborative projects are as follows.

[KPIs to be achieved by FY2015]

- Construct a full genome database for pathogens based on the establishment of a system for the sharing of global pathogen and clinical information, shed light on their physiological and clinical manifestation, and prepare a pathogen map for Asia (to improve the performance of public health measures to combat influenza, dengue fever, infectious diarrhea, and drug-resistant bacteria)

[KPIs to be achieved by around 2020]

- Identify drug target sites based on whole-genome databases obtained for pathogens (influenza, dengue fever, infectious diarrhea, drug-resistant bacteria); develop and put into practical application new rapid diagnosis methods
- Conduct clinical research and trials for a norovirus vaccine and an intranasal influenza vaccine, and apply for pharmaceutical approval for these

[KPIs to be achieved by around 2030]

- Develop new vaccines
(E.g. versatile influenza vaccines)
 - Develop new antibiotics and antivirals, etc.
 - Eradicate/eliminate infectious diseases such as polio and measles, working in partnership with the WHO and various other countries
(KPI to be achieved by 2050 in the case of tuberculosis)
- Emerging/Re-emerging Infectious Disease Project of Japan
 - Focusing on various pathogens both within Japan and overseas, including influenza, tuberculosis, infectious diseases of animal origin, drug-resistant bacteria, and HTLV-1 (human T-cell lymphotropic virus type 1), the government will conduct epidemiological studies, basic research, and research aimed at improving the effectiveness and safety of vaccination, and will adopt an integrated approach in promoting measures to combat infectious disease, as well as the development of diagnostic drugs, therapeutic drugs, and vaccines.
 - The government will build a full genome database concerning pathogens within Japan and overseas, in order to share pathogen information in real time and facilitate international risk assessment of infectious diseases. Moreover, by analyzing the information amassed, it will encourage a swift response in the event of an infectious disease epidemic, including the implementation of targeted surveillance.

Furthermore, in light of the Basic Plan on Vaccination, the Guidelines on the Prevention of Specific Infectious Diseases, and the Stop TB Japan Action Plan, among others, the government will develop new diagnostic drugs, therapeutic drugs, and vaccines by identifying the areas of pathogens targeted by drugs. Through these efforts, it will be able to contribute to the prevention, diagnosis, and treatment of infectious diseases not only in Japan, but also at the site of outbreaks overseas.

 - To promote efforts to cultivate young researchers in the field of infectious diseases, the government will implement training programs at the overseas centers of the Japan Initiative for Global Research Network on Infectious Diseases (J-GRID) and at the National Institute of Infectious Diseases.
 - In response to the adoption in May 2014 of a new WHO strategy on measures to combat tuberculosis, the government will promote research into tuberculosis, to ensure Japan's inclusion in the ranks of low prevalence countries by 2020.
 - Ahead of the 2020 Tokyo Olympics and Paralympics, the government will promote research aimed at strengthening surveillance of infectious diseases.

<Intractable diseases>

In fields in which research is not progressing, due to the fact that there are few sufferers of the diseases in question, the government will provide seamless financial support based on interministerial collaboration throughout the whole research process, with the aim of conquering rare and intractable diseases. Through this, it will aim to shed light on the pathology of intractable diseases, as well as promoting integrated efforts to develop effective new therapeutic drugs and expand the applications of existing drugs. The KPIs and interministerial collaborative projects are as follows.

[KPIs to be achieved by FY2015]

- License out at least 7 new clinical trials with a view to pharmaceutical approval

(Severe pulmonary hypertension, Creutzfeldt-Jakob disease and other prion diseases, etc.)

[KPIs to be achieved by around 2020]

- Approve new drugs and additional indications for existing drugs in at least 11 cases

(ALS, distal myopathy, etc.)

- Promote collaborative international clinical research and trials in partnership with U.S. and European databases

● Rare/Intractable Disease Project of Japan

- With the aim of conquering rare and intractable diseases, the government will promote research focused on identifying the etiology and pathophysiology of new diseases that could lead to the development of new therapies, and research aimed at developing groundbreaking diagnostic techniques, therapies, and preventive measures with a view to the practical application of drugs and medical devices, etc.

In addition, it will aim to feed the results of research into iPS cells, etc. back to society without delay through efforts to shed light on the onset mechanism of diseases using disease-specific iPS cells, as well as by promoting drug discovery research and the development of preventive measures and therapies.

○ Other R&D required to promote the Healthcare Policy

Giving adequate consideration to the needs of patients and society, as well as medical and economic needs, the government will promote the development of preemptive medicine, new drugs, diagnostic techniques, and treatment methods, and medical devices, targeting a wide range of diseases. These include diabetes and other lifestyle-related diseases; stroke and other cardiovascular disorders; respiratory diseases; musculoskeletal and connective tissue disorders, and urinary tract disorders; conditions

that substantially reduce the quality of life of elderly people; pediatric and perinatal diseases, which affect the next generation of citizens; AIDS; and hepatitis.

(3) Developing and utilizing common infrastructure

The government will promote the creation and maintenance of databases focused on diseases, including rare and intractable diseases, as well as securing the infrastructure required to bring evidence-based medicine to fruition, such as the linkage and utilization of various genome banks and cohorts. In addition, it will steadily promote the integration of databases focused on the life sciences.

In addition to further utilization of drug discovery support infrastructure on a nationwide basis, centering on the Drug Discovery Support Network, the government will promote the utilization of common science and technology infrastructure by promoting the use by researchers in industry, academia, and government of various facilities and equipment that form the infrastructure for advanced research, including advanced large-scale research facilities, supercomputers, and advanced measurement and analysis instruments. Moreover, to encourage the development of medical device via collaboration between medicine and industry, the government will establish a system that will enable multiple specialist support organizations to support the development of such device (the Medical device Development Support Network (tentative name)).

Accordingly, the government will implement the following measures.

- Integration of life science databases
 - To integrate databases concerning research in the life sciences, the government will promote R&D focused on data integration and search techniques and will put in place cross-cutting information infrastructure.

- Support for R&D provided by the Drug Discovery Support Network to promote new drug discovery (described above: II. 1. (1) (a))

- Promoting the effective use of shared science and technology infrastructure
 - The government will support research at universities, etc. by building advanced, shared drug discovery and medical technology support infrastructure, including technologies and facilities that will assist in drug discovery and other life science research.
 - With a view to advancing research in the life sciences, the government will

strategically collect and store important, high-quality bioresources at key centers, and will make these available to research institutes.

- It will develop academic information networks that will form the infrastructure for promoting the utilization of advanced large-scale research facilities and supercomputers, etc.
- The government will upgrade academic information networks to ensure interoperability between systems handling medical information (described above: II. 1. (4)).

(4) The positioning of core hospitals for clinical research in the Medical Care Act

Core hospitals for clinical research are positioned in the Medical Care Act as playing a central role in conducting world-class clinical research and physician-led clinical trials. To promote the high-quality clinical research and trials required for Japan to develop innovative drugs and medical devices, the government will lose no time in considering the requirements for core hospitals for clinical research from the following perspectives, so that these hospitals can be established.

- (a) The ability to ensure the functions required of a core hospital for clinical research throughout the hospital, under the leadership of the hospital management
- (b) The ability to formulate and establish an appropriate research plan with a view to the exit strategy, and to conduct clinical research in compliance with ICH-GCP
- * In the case of medical device, compliance with ISO 14155:2010. The same shall apply hereinafter.
- (c) The ability to conduct ethical reviews that are highly transparent and appropriate from the perspective of ethics, science, safety, and reliability
- (d) The ability to guarantee the integrity of data in compliance with ICH-GCP
- (e) The ability to manage intellectual property and conduct technology transfer in relation to seeds
- (f) The ability to plan and formulate high-quality, joint multi-institutional clinical research and trials, and to implement these in partnership with other medical institutions. In addition, the ability to provide support as a core hospital for clinical research and trials being undertaken by other medical institutions
- (g) The ability to provide education to the relevant individuals and to conduct PR and awareness-raising activities targeting patients and the public as a whole

Accordingly, the government will implement the following measures.

- Status of deliberations concerning the positioning of core hospitals for clinical research in the Medical Care Act

- The Bill on Promoting Efforts to Ensure Comprehensive Provision of Medical Care and Long-Term Care was passed and enacted in the Diet on June 18, 2014. As a result, the legal standing of core hospitals for clinical research was established in the Medical Care Act for the first time. Currently, those hospitals being developed under the Project for Japan Translational and Clinical Research Core Centers (such as centers for early and exploratory clinical trials, and core hospitals for clinical research) that meet certain requirements can be called core hospitals for clinical research, once approval from the Minister of Health, Labour and Welfare is forthcoming.

- It is envisaged that, as well as conducting high-quality clinical research and trials themselves, these core hospitals for clinical research established in accordance with the Medical Care Act will have ARO functions to support the planning and implementation of clinical research and trials at other facilities. Accordingly, the government will utilize these to conduct research into seeds from translational research support centers and research in areas where there is a high level of need from a medical perspective, but where development by companies has not been forthcoming. By building up evidence through such research, the government will promote the creation of innovative drugs, medical devices, etc. and medical technology. Furthermore, it will aim to establish a system that can adequately respond to any adverse events that occur when conducting clinical research and trials using unapproved drugs.

III. Requirements for Intensive and Systematic Promotion of Medical R&D Measures

1. Follow-up

Progress in implementing this Plan will be reviewed as required, within at least five years or thereabouts, taking into account changes in the situation surrounding medical R&D and evaluations of the effects of medical R&D measures. Based on the results, this Plan will be reviewed and any necessary changes will be made.

Appendix: Glossary

- ALCOA principles

Five basic requirements prescribed in the FDA's guidance concerning the quality of source documents in research: Attributable, Legible, Contemporaneous, Original, and Accurate

- ARO: Abbreviation of Academic Research Organization

An organization equipped with functions that universities, etc. with research institutes and medical institutions can use to support drug development

- CRC: Abbreviation of Clinical Research Coordinator

An expert who provides support in the smooth running and management of tasks associated with clinical research and trials. CRCs serve as coordinators between trial subjects, physicians, and trial sponsors at medical institutions conducting clinical research and trials, and are involved in all duties associated with clinical research and trials that do not require medical judgment.

- DDS: Abbreviation of Drug Delivery System

A system that controls the delivery of drugs within the body in terms of quantity, space, and time

- ELSI: Abbreviation of ethical, legal and social implications

- FDA: Abbreviation of Food and Drug Administration (a U.S. government agency)

- FIH: Abbreviation of First in Human

The first administration (use) of a drug or item of medical device, etc. in a human in a clinical research or trial

- GCP: Abbreviation of Good Clinical Practice

This prescribes the requirements for the proper scientific conduct, based on adequate ethical considerations, of clinical research and trials carried out to gather the data and materials that must be submitted when applying for approval for a drug or item of

medical device, etc.

- GLP: Abbreviation of Good Laboratory Practice

This prescribes the requirements with which facilities conducting tests must comply in order to ensure the integrity of data from safety tests on animals, which are obtained for submission as part of an application for approval for a drug or item of medical device, etc.

- GMP: Abbreviation of Good Manufacturing Practice

These are criteria for process control in manufacturing, to ensure that products are made safely and that certain quality standards are maintained throughout all processes, from delivery of ingredients and raw materials, through to manufacture and shipping

- ICH: Abbreviation of International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

An international conference involving Japan, the U.S., and the EU

- ICT: Abbreviation of Information and Communication Technology

- PMDA: Abbreviation of Pharmaceuticals and Medical Devices Agency

With the aim of helping to improve the health of the public, the PMDA provides rapid redress for health hazards due to side-effects from drugs; reviews the quality, effectiveness, and safety of drugs and medical devices, etc.; and gathers, analyzes, and disseminates information concerning safety once these items become commercially available.

- TR: Abbreviation of Translational Research

Translational research is conducted to link the results of basic research into the development of diagnostics and therapies

- Gene therapy

Treatment provided by administering into the human body a gene or cells into which a gene has been introduced in vitro

- Epigenome

A collection of information about the mechanism that determines the way in which genes work, without changing the base sequence of DNA (epigenetics)

- Open innovation

The resolution of problems through the use of external development capabilities and ideas, creating entirely new value

- Omics

The comprehensive study of all molecules in the human body

- Genome

A word created from a combination of the words gene and chromosome, meaning all genetic information in DNA

- Genomic medicine

Medical treatment that uses human genetic information (genomic information) to predict drug response and side-effects in individual patients, and to facilitate prevention based on a forecast of morbidity in each patient

- Genome-based drug discovery

The development of new drugs by estimating the stereostructure of proteins that are targeted by drugs, based on genomic information

- Companion diagnostics

In vitro diagnostic drugs that are used to improve the effectiveness or safety of a specific drug, which are essential when using the drug in question (excludes in vitro diagnostic drugs whose sole objective is to diagnose disease)

- Clinical trial

Clinical trials are implemented with the aim of gathering data that can be submitted as test results, along with other materials that must be submitted when applying for approval to manufacture or sell a drug or item of medical device, etc.

- Drug repositioning

The use of comprehensive efficacy profiling of existing medications and compounds demonstrating new pharmacological actions whose development has been discontinued,

in order to search for new indications and develop these medications as drugs with new effects

- Biopharmaceuticals

Drugs in which the active ingredient has been created from biological agents, such as proteins derived from cells, viruses, bacteria or other organisms (e.g. growth hormones, insulin, antibodies, etc.)

- Bioinformatics

A field of study focused on using techniques from computer science to analyze biological data, and the technologies used for this analysis

- Biomarker

A characteristic value that can be objectively measured and evaluated, which is an indicator of a normal biological process, pathological process, or a pharmacological response to a therapeutic treatment

- Bioresource

A laboratory animal, plant, cell, gene, or microorganism, etc. used in research

- Peer review

Review by multiple researchers with a very similar field of expertise

- Nonclinical test

A test using animals or an in vitro test using cultured cells, etc., which is carried out to obtain scientific data to evaluate and prove quality, effectiveness, and safety, in order to allow a study to move on to clinical research and trials

- Clinical research

Medical research with human subjects that is carried out for the purpose of improving methods of preventing disease, diagnostic methods, and treatment methods, understanding the causes and pathology of disease, and improving the quality of life for patients

- Regulatory science

A branch of science that aims to make accurate, evidence-based projections, appraisals,

and judgments, in order to ensure that the fruits of science and technology take the most desirable form from the perspective of their harmonization with people and society, with the objective of ensuring that the results of R&D in this area benefit people and society as a whole. (Fourth Science and Technology Basic Plan) In particular, in the fields of drugs and medical devices, etc., science focused on swift, appropriate forecasting, evaluation, and judgment based on scientific knowledge, concerning the quality, effectiveness, and safety of practical applications for medical R&D results (Article 13 (2) of the Act on Promotion of Healthcare Policy).