FY2017

Advanced Research and Development Programs for Medical Innovation (AMED-CREST, PRIME)

Application Guidelines

April 2017

Division of Emerging Research
Department of Research Infrastructure
Japan Agency for Medical Research and Development (AMED)

Ⅰ. Introduction

The R&D projects being solicited in accordance with these Application Guidelines are R&D projects being solicited under Advanced Research and Development Programs for Medical Innovation (AMED-CREST, PRIIME), which is administered by the Japan Agency for Medical Research and Development (hereinafter referred to as "AMED").

1. Program Outline

With the goal of developing innovative drugs, medical devices, and medical technologies under R&D objectives determined by the government, researchers in universities and other institutions are invited to submit R&D proposals upon which a limited-time R&D system transcending organizational frameworks for driving R&D activities will be constructed. The program promotes advanced R&D for generating and nurturing breakthrough technologies and know-how (innovative), while also accelerating and deepening R&D that yields promising results.

This program comprises three types of research: unit-type (AMED-CREST), solo-type (PRIME) and incubate-type (LEAP)*. For AMED-CREST and PRIME, AMED specifies the R&D pursuit areas and the Program Supervisors and Program Officers for leading the research under "Research and Development Objectives" designated by the national government. Through management by Program Supervisors and Program Officers and cooperation in each R&D area, the program aims to construct a R&D system transcending organizational frameworks as well as draw out the maximum potential of the research. AMED-CREST focuses on achieving world-class R&D results aimed at generating innovative seeds, with the respective R&D being conducted by a unit (a group of researchers) that is led by a R&D Principal Investigator (PI). PRIME aims to generate R&D results that will spawn innovative seeds, with the R&D being independently conducted by the individual R&D PI.

*: LEAP targets the swift commercialization of research results that are promising but where the risk of development is difficult for companies to evaluate. No solicitation is performed in LEAP.

Proactive Participation and Activity by Young Researchers

The aim of this program is to generate epoch-making seeds in fields such as innovative drugs, medical devices and medical technologies and so on. Global competition is becoming ever more fierce in the area of medical research and development, and the activities of young researchers are essential in order for Japan to maintain the highest level of medical research and development in the world now and in the future.

PRIME is a program under which researchers pursue research on an individual basis. We provide support for young researchers to further deepen and accomplish their original and creative ideas through the activities of this program. We expect R&D concepts that are well-thought out and in which researchers collect and analyze the latest information and experimental results without becoming trapped in the present day frameworks. Program Supervisors (PS), Program Officers (PO) and other advisers provide advice in order not only to realize the proposed R&D concepts but also to develop the medical application of research results. Moreover, the R&D fields in the program are currently organized working as a collaborative system that goes beyond the bounds of ordinary scientific societies in order to attain the R&D objective. PRIME is becoming an appealing forum where it is possible to interact and collaborate with researchers of the highest repute in other fields, something that cannot be done in usual academic associations. Moreover, AMED-CREST and PRIME R&D projects work together, and opportunities are provided to build networks not only among PRIME researchers but also with AMED-CREST researchers. We hold high expectations that young researchers will proactively put forward ideas to PRIME with a view towards achieving sustainable development in the field of medical research.

We also hope that the AMED-CREST R&D projects will see the participation of many promising young researchers, and that through the projects human resources responsible for the next generation will be fostered. We would like the R&D Principal Investigators of AMED-CREST to help young researchers master the latest R&D technologies and also instruct them in a manner that allows them to be able to think for themselves, conduct experimental verifications and reach robust conclusions.

We will support all young researchers in their efforts to make their excellent ideas contribute to the development of medical care and the health and welfare of the general public. Finally, it is our hope that all the young researchers will propose the projects and join in the program, and make great strides forwards to become leading figures in their R&D areas.

Makoto Suematsu, MD, PhD
President, Japan Agency for Medical Research and Development

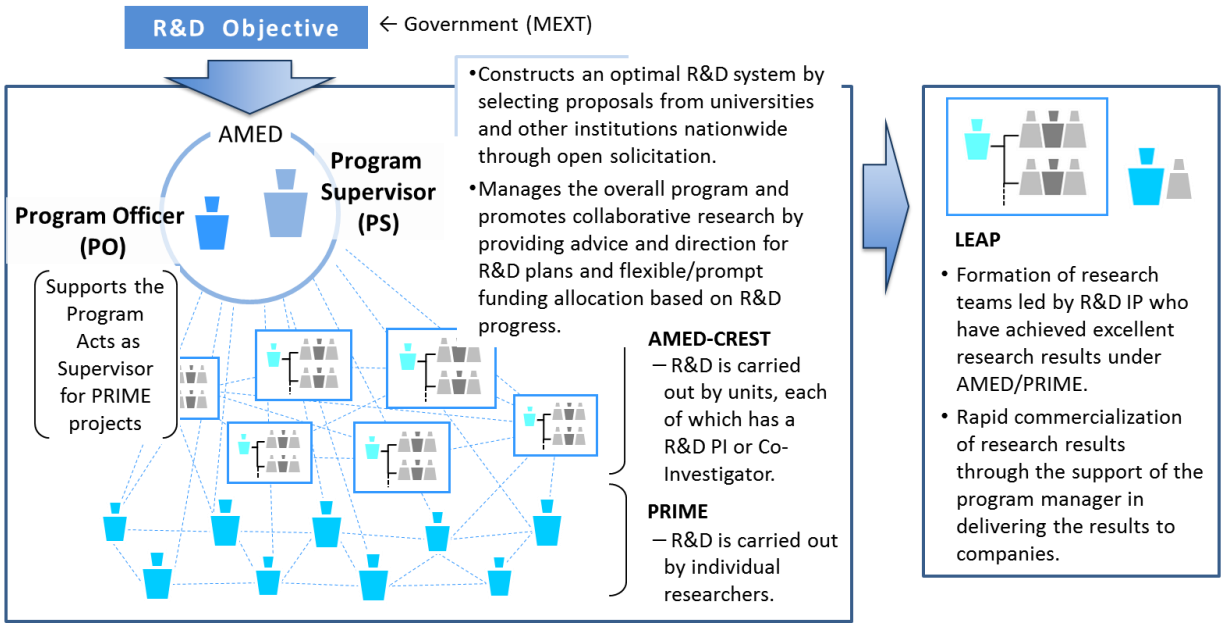
2. Program Structure

(1) Program Implementation System

In accordance with the "Plan for Promotion of Medical Research and Development", a Program Supervisor (hereinafter referred to as "PS") and Program Officer (hereinafter referred to as "PO") are assigned to the Program to ensure efficient utilization of competitive research funds and generation of excellent research accomplishments.

The PS and PO have complete knowledge and understanding of the progress status of the program overall and provide the necessary guidance and advice to ensure that the program runs smoothly. Furthermore, research institutes and researchers are obligated to cooperate with the PS and PO. Based on the guidance and advice provided by the PS and PO, researchers may be required to revise, change, or suspend their R&D project plans or change their project implementation system if this is deemed necessary.

To accomplish the R&D Objectives designated by the national government (Ministry of Education, Culture, Sports, Science and Technology), the Program Supervisor (PS) and Program Officer (PO) construct a time-limited system for conducting R&D by organizing a R&D area, assembling an optimal mix of researchers from existing institutions and research projects—namely industry, academia and government—and oversee work in the R&D area with the cooperation of R&D Area Advisers and others. R&D PIs for AMED-CREST and PRIME receive support from the PS and PO in accordance with their operating policies as they advance the R&D projects they have proposed with the aim of generating innovative seeds in accordance with R&D Objectives of the management policies of the PS and PO, while actively building and utilizing personal networks through dialog with R&D Area Advisers and others, and coordination with participating researchers and connections with others both in Japan and overseas.



(2) R&D Period and R&D Costs

As a general rule, the R&D period and budget for one R&D project are shown below. In some cases, budget ranges may be set independently for individual R&D areas, so be sure to refer to "XI. R&D Area being Solicited" for details.

Program	R&D Period	R&D Costs (entire direct cost)
AMED-CREST	Up to five-and-a-half years	150 million yen to 500 million yen per research project
PRIME	Up to three-and-a-half years	30 to 40 million yen per research project

Under contract R&D agreements, AMED generally pays research institutions a separate amount for overheads (indirect costs) of up to 30% of R&D costs (direct costs).

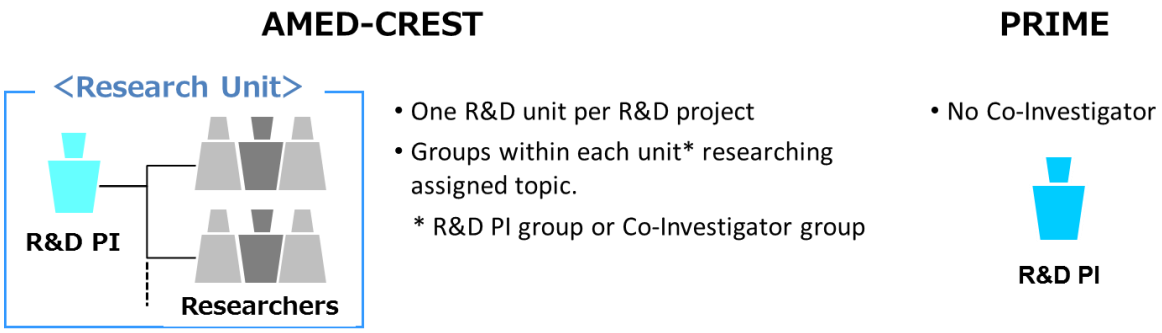
(3) R&D Unit Organization

(a)AMED-CREST

In AMED-CREST, the R&D PI can bring multiple industrial and academic Principal Investigators (PI) together optimally in a unit with the aim of realizing the R&D PI's proposed research initiative in accordance with the R&D objectives and management policies of the PS and PO. The R&D PI carries out R&D that contributes to the goals of the overall R&D area while bearing full responsibility for the R&D project which he/she is leading. For further details on R&D unit organization requirements, refer to II.2.

(b)PRIME

The PRIME R&D PI takes responsibility for implementing their own R&D projects and carrying out R&D that will contribute to the goals of the overall R&D area with the aim of realizing the R&D PI's proposed research initiative in accordance with the R&D objectives and management policies of the PS and PO. Please note that Co-investigators cannot be assigned to PRIME R&D projects.



(c)Roles of Principal Institutions and Subsidiary Institutions

Under this program, R&D projects shall be implemented by Principal Institutions or, if necessary, Subsidiary Institutions

(a) "Principal Institution" refers to the research institute* with which the R&D Principal Investigator (PI) is affiliated and which has concluded a direct contracted R&D agreement with AMED.

(b) "Subsidiary Institution" refers to a research institute* other than the Principal Institution with which a Co-Investigator is affiliated and which has concluded a subcontracted R&D agreement with the Principal Institution.

*For details regarding contracted R&D agreements with institutions under this program, please refer to Chapter V.

Ⅱ. Application Requirements

Please ensure that you understand these requirements for submitting proposals.

* In principle, if it has been determined that a R&D proposal does not fulfill the submission requirements, the R&D proposal will be neither accepted nor selected.
* If a submitted R&D proposal is selected, the R&D project must continue to fulfill the submission requirements for the entire duration of the R&D period. If the R&D project ceases to meet these requirements, the R&D project will, in principle, be completely or partially suspended (i.e. terminated early.)

1. Eligible Applicants

(a) Applicants must be the person who will be the R&D PI for the project.
(b) Applicants must be affiliated with a domestic Japanese research institution[*1], and in general, they will organize a system for carrying out the proposed R&D at this institution. (May be any nationality.)
  * In principle, personnel expenses for PI and Co-PI shall be paid by their research institution. In details about personnel expenses, please refer to V. 2. (1).
(c) Researchers who are able to bear overall responsibility for an R&D project throughout the entire R&D period.
  * For further details, please refer to V. 6.
(d) For both AMED-CREST and PRIME, an applicant must be the originator of the proposed R&D initiative and a researcher who will independently perform R&D work aimed at realizing the R&D initiative.

*1: Eligible Applicants for this program shall be researchers affiliated with a research institute in Japan that fulfills the conditions shown in (1)–(5) below and who have the capability to take responsibility for formulating an R&D implementation plan and compiling the research accomplishments for the R&D project for which the application is being submitted (hereinafter referred to as "R&D Principal Investigator" (PI)).

(1) "Research Institute" refers to institution with the characteristics shown in (a)–(g) below.
  (a) National facility or other organization[1] (limited to institutions/facilities where the PI is employed in an educational position, research position, medical care position[2], welfare service position[2], or designated position[2], or as a fixed-term contract researcher).
  (b) Research institute, etc., affiliated with a local public body.
  (c) University as prescribed under the School Education Act (Law No. 26 of 1947) or university affiliated research institute, etc. (including inter-university research institute corporations).
  (d) R&D division or research laboratory, etc. of a private enterprise
  (e) A special private corporation, general incorporated association, general incorporated foundation, public interest incorporated association, or public interest incorporated foundation (hereinafter referred to as a "special private corporation, etc.") whose main activity purpose is research.
  (f) An independent administrative corporation as prescribed under Article 2 of the Act on General Rules for Incorporated Administrative Agencies (Act No. 103 of 1999) or local incorporated administrative agency as prescribed under Article 2 of the Act on Local Incorporated Administrative Agencies (Act No. 118 of 2003) whose main activity purpose is research.
  (g) Other institution deemed appropriate by the President of AMED.

  [1]Refers to a research institute, inspection and certification institute, educational and training facility, medical and rehabilitation facility, reformatory and internment facility, or work facility affiliated with a government organization as prescribed by the Cabinet Office and under Article 3 Paragraph 2 of the National Government Organization Act

  [2]Limited to persons affiliated with a hospital or institution that conducts research.

(2) In the case that the project is selected, the research institute's facilities and equipment can be used for carrying out the project.
(3) In the case that the project is selected, the research institute is able to carry out administrative procedures such as contract procedures.
(4) In the case that the project is selected, the research institute is capable of responsibly handling any intellectual property (IP) rights (including patents and copyright, etc.) generated through implementation of this program.
(5) The research institute is capable of continuing to promote R&D even after this program has concluded, and can carry out the necessary procedures, etc., for supporting researchers in relation to this program.

In only PRIME, in the case that a researcher who is not affiliated with a designated research institute or is affiliated with a research institute outside of Japan is selected as the PI, the researcher may apply for this program if they are able to become affiliated with a research institution in Japan and create a system for conducting research by October

1st 2017. However, in the case that the above conditions are not met by October 1st 2017, as a general rule the decision to adopt the R&D project shall be cancelled.

Furthermore, in order to confirm the research institute's ability to fulfill the contracted R&D agreement, at the time of the application review, the Principal Institution or Subsidiary Institution may be required to submit materials regarding the content of major projects undertaken by the institution and its finances (assets, debts, etc.).

2. Requirements for Organizing a R&D Project

The following requirements only apply to AMED-CREST R&D proposals:

a. An R&D unit is the optimal organizational approach for pursuing the R&D initiatives of the applicant.
b. When a Co-investigator is assigned to the R&D project, the Co-investigator plays an essential role in realizing the R&D initiatives and can significantly contribute to achieving the R&D goals.
c. Principal Institution must conclude a subcontracted R&D agreement with Subsidiary Institution appropriately.
d. When a research institution is overseas, it must meet the following additional conditions:

- The participation of a researcher affiliated with an overseas research institution as a R&D Co-PI in an R&D project is contingent on whether the R&D initiatives can only be realized with the participation of the overseas institution (and requires Program Supervisor approval.)
- The overseas research institution is required to transfer, free of charge, intellectual property rights to AMED. (Article 19 of the Industrial Technology Enhancement Act (Act No. 44 of 2000) (Japanese version of the Bayh-Dole Act) does not apply to overseas research institutions.)
- The overseas institution must be able to properly execute the budget in accordance with the R&D agreement or AMED's budget execution policy if such has been specified by AMED, and must be able to submit a detailed statement of R&D expenses to AMED (equivalent to the balance book of Japanese institutions) prepared in English.
- Payments to the overseas research institution for overheads (indirect costs) must not exceed 30% of the direct costs.

* When it is desired that one or more overseas research institutions be included in an R&D unit, please note on the R&D proposal (Form 13) the reasons why the participation of a Co-investigator affiliated with an overseas research institution is required.

3. Limitations on Duplicate Applications within the Program

- Researchers can submit a proposal for only one solicitation for AMED-CREST/PRIME participation described in this application guideline.
- Current R&D PIs of the Advanced Research and Development Programs for Medical Innovation cannot be appointed as R&D Co-Invstigators (with the exception of cases in which the PRIME R&D project term is to be reached by the end of FY 2017).
- Multiple applications by the same research team whereby the R&D PI and R&D Co-Investigators interchange roles are not permitted for AMED-CREST.
- Under AMED-CREST making a current PRIME R&D PI an R&D CO-Investigators is not permitted (this does not, however, apply in the event that the conclusion of the PRIME R&D term is within FY 2017).
- If multiple selected proposals in the Advanced Research and Development Programs for Medical Innovation involve the same R&D Co-Investigators (Applicant) and participants (or candidates), adjustments such as reducing R&D costs or selecting only one of the Applicant's proposed R&D projects may be made by taking the content and scale of the R&D proposals into consideration.
- If the Applicant for PRIME is also a R&D Co-Investigators or participant (or candidate) for a proposal submitted to AMED-CREST and both proposals are shortlisted, adjustments such as revising the applicant's position in the proposed R&D project under AMED-CREST or selecting only one of the R&D projects proposed by the Applicant may be made.
- The Appilicant who is R&D Co-Investigator in AMED-CREST can submit a proposal to PRIME. If the Applicant is shortlisted as a candidate in PRIME, the Applicant may choose to withdraw the proposal for PRIME or to reconsider the role as R&D Co-Investigator.

4. Conflicts of Interest Involving Applicants and the Program Supervisor/Program Officer

An acceptance plan for each R&D proposal is prepared by the Program Supervisor (PS) in the case of AMED-CREST and by the Program Officer (PO) in the case of PRIME. (Please refer to pervisor/Program Officeroposal submitted to AMED-CREST and both p.) To ensure fair and transparent selection, Applicants will be excluded from selection consideration in the case that any of conditions a. through d. below applies. When it is unclear whether or not a condition applies, please contact AMED (X. References), before submitting your R&D project proposal.

(1) Application to AMED-CREST

1) The evaluatee is a family member/relative of the Project Evaluation PS.
2) The evaluatee and PS are both affiliated with the same smallest organizational unit (e.g. same research lab) of a university, national government-funded research institution or other research institution, or the applicant and PS are affiliated with the same company.
3) The evaluatee and PS are presently working in close cooperation on the same joint research project, or have done so within the past five years. (For example, the evaluatee and PS worked on a joint research project, co-authored a research paper, worked toward the same objectives as members of the same research team, performed different parts of a research project managed by the PS, or were otherwise essentially affiliated with the same research group.)
4) The evaluatee and PS were in a close teacher-student relationship for a total of more than 10 years (not necessarily continuous), or in a direct employer-employee relationship. "Close teacher-student relationship" means cases in which the evaluatee and PS were affiliated with the same research lab as well as periods during which the PS, although affiliated with a different organization, essentially functioned as a research adviser for the evaluatee.
5) The evaluatee has received economic benefits from PS within the past three years, including the fiscal year in which the Project Evaluation Panel evaluation is conducted, of more than one million yen.
6) Other serious conflicts of interest are recognized to exist.

(2) Application to PRIME

1) The evaluatee is a family member/relative of the Project Evaluation PO.
2) The evaluatee and PS are both affiliated with the same smallest organizational unit (e.g. same research lab) of a university, national government-funded research institution or other research institution, or the applicant and PO are affiliated with the same company.
3) The evaluatee and PO are presently working in close cooperation on the same joint research project, or have done so within the past five years. (For example, the evaluatee and PS worked on a joint research project, co-authored a research paper, worked toward the same objectives as members of the same research team, performed different parts of a research project managed by the PS, or were otherwise essentially affiliated with the same research group.)
4) The evaluatee and PO were in a close teacher-student relationship for a total of more than 10 years (not necessarily continuous), or in a direct employer-employee relationship. "Close teacher-student relationship" means cases in which the evaluatee and PS were affiliated with the same research lab as well as periods during which the PO, although affiliated with a different organization, essentially functioned as a research adviser for the evaluatee.
5) The evaluatee has received economic benefits from PO within the past three years, including the fiscal year in which the Project Evaluation Panel evaluation is conducted, of more than one million yen.
6) Other serious conflicts of interest are recognized to exist.

5. Important Items Regarding Application

(1) Contracted R&D Agreements

In implementing selected R&D projects, as a general rule* a contracted R&D agreement shall be concluded between the head of the research institute carrying out the R&D project and the President of AMED.

R&D PIs, together with research institutions, shall appropriately manage (expenditure planning, monitoring, etc.) overall R&D budgets for R&D units. The R&D Co-PI together with research institutions which will conclude a contract R&D agreement with AMED shall appropriately manage (expenditure planning, monitoring, etc.) R&D budgets for his/her own R&D unit.

*For details, please refer to Chapter V.

(2) Cross-ministerial Research and Development Management System (e-Rad)

For contracted R&D funds, applications shall be accepted via the Cross-ministerial Research and Development Management System (hereinafter referred to as "e-Rad"), which places certain processes related to R&D management centered on competitive research funding systems. In submitting an application, please be sure to carefully read the program outline, the outline of R&D projects for which applications are being solicited, and other information provided and thoroughly consider the kinds of results your proposed R&D project can produce before completing the proposal documents. For details, please refer to Chapter IV.

(3) Registration with a Clinical Research Registration System

In the case that an intervention study is to be conducted, in accordance with the "Ethical Guidelines for Medical and Health Research Involving Human Subjects", please register the project with one of the three clinical research registration systems listed below prior to commencement of the relevant clinical research (you may be required to submit a report indicating whether or not the project has been registered (free format) at the time that you submit your contracted R&D accomplishments report). Please note that investigations shall be carried out to ensure that there are no discrepancies between the registered project content and the content of the research being conducted.

1) University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN-CTR)
http://www.umin.ac.jp/ctr/index-j.htm
2) Japan Pharmaceutical Information Center (JAPIC) Clinical Trial Information
http://www.clinicaltrials.jp/user/cte_main.jsp
3) Center for Clinical Trials, Japan Medical Association (JAMACCT) Clinical Trial Registry
https://dbcentre3.jmacct.med.or.jp/jmactr/

6. Security Trade Control (Countermeasures to Technology Leakage Overseas)

At research institutes, a large quantity of cutting-edge research is carried out. At universities in particular, with the increase in international students and foreign researchers due to internationalization, there is an increasing risk of cutting-edge research and/or research materials/equipment flowing out of Japan and being misused for the development/production of weapons of mass destruction or for other improper uses. For this reason, it is imperative that in carrying out various type of research activities—including contracted R&D under this program—research institutes implement systematic measures to ensure that research accomplishments that could be used for military purposes do not fall into the hands of persons suspected of being involved in the development of weapons of mass destruction or with terrorist organizations or other concerning activities.

In Japan, export regulations* are enforced in accordance with the Foreign Exchange and Foreign Trade Act (Law No. 228 of 1949) (hereinafter referred to as the "Foreign Exchange Act"). Accordingly, in the case that a person wishes to export (provide) goods or technology prescribed under the Foreign Exchange Act, as a general rule they are required to obtain the permission of the Minister of Economy, Trade and Industry. Please be sure to comply strictly with all laws, ministerial ordinances, and directives, etc., issued by various Japanese government ministries and agencies, beginning with the Foreign Exchange Act. IN the case that R&D is carried out in infringement of relevant laws or guidelines, allocation of R&D funds may be suspended and the decision to allocate R&D funds may be cancelled.

*Currently, under Japan's security export control system, there are two types of regulations based on international agreements: (1) a system under which the permission of the Minister of Economy, Trade and Industry must generally be obtained in the case that a person wishes to export (provide) goods (technology) with specifications or functions above a certain level—mainly carbon-fiber and numerically controlled machine tools, etc.—("List Regulations", and (2) a system under which the permission of the Minister of Economy, Trade and Industry must generally be obtained in the case that a person wishes to export (provide) goods (technology) to which List Regulations do not apply and which fulfill certain conditions (use, demand, inform conditions) (Catch-all Regulations).

Not only the export of goods but also the provision of information is subject to regulations under the Foreign Exchange Act. When providing List Regulation technology to a foreign national (non-resident of Japan), permission must be received in advance. "Provision of technology" includes not only the provision of blueprints/designs, specifications, manuals, samples, prototypes, and other technological information via paper, e-mail, CD, USB flash drive, or other storage medium but also the provision of operational knowledge through technological guidance or skills training and technological support at seminars, etc. There are cases in which large amounts of technological exchange that could be subject to regulation under the Foreign Exchange Act may be included in joint research activities or when international students are involved.

On the Ministry of Economy, Trade and Industry website, details regarding security trade control are provided. Please refer to the following for further details (in Japanese).

- Ministry of Economy, Trade and Industry: Security Trade Control (general)
  http://www.meti.go.jp/policy/anpo/
- Ministry of Economy, Trade and Industry: Handbook for Security Trade Control (8th edition, 2014)
  http://www.meti.go.jp/policy/anpo/seminer/shiryo/handbook.pdf
- Center for Information on Security Trade Control
  http://www.cistec.or.jp/
- Guidance for Management of Sensible Nuclear Technology (SNT) in Relation to Security Trade Control (for universities/research institutes)
  http://www.meti.go.jp/policy/anpo/law_document/tutatu/t07sonota/t07sonota_jishukanri03.pdf

Ⅲ. Application/Selection Implementation Methods

1. Outline of R&D Projects for which Applications Are Being Solicited

The outline of the R&D projects for which applications are being solicited included in these Application Guidelines is as follows. For details regarding individual R&D projects being solicited, please refer to Chapter XI.

#	R&D Area (PS/PO)		Scale of R&D funds	Period in which R&D is Scheduled to be Implemented	Planned Number of New Awarded Projects
1	Clarification of the mechanism of individual functional impairment over the entire life course (Program Supervisor (PS):Eisuke Nishida) (Program Officer (PO):Eiji Hara)	AMED-CREST	Max of 390 million yen total period for each project (including indirect costs)	Max. of 5.5 years FY2017–FY2022	Around 3–6 project
		PRIME	Max of 52 million yen total period for each project (including indirect costs)	Max. of 3.5 years FY2017–FY2020	Around 8–12 project
2	Understanding the interactions and symbiosis between the microbiome and the host organism, leading to an understanding of the mechanisms of disease onset (Program Supervisor (PS): Chihiro Sasakawa) (Program Officer (PO): Hiroshi Ohno)	AMED-CREST	Max of 390 million yen total period for each project (including indirect costs)	Max. of 5.5 years FY2017–FY2022	Around 2–4 project
		PRIME	Max of 52 million yen total period for each project (including indirect costs)	Max. of 3.5 years FY2017–FY2020	Around 8–10 project
3	Elucidation of Mechanobiological Mechanisms and Their Application to the Development of Innovative Medical Instruments and Technologies (Program Supervisor (PS): Masahiro Sokabe) (Program Officer (PO): Joji Ando)	AMED-CREST	Max of 390 million yen total period for each project (including indirect costs)	Max. of 5.5 years FY2017–FY2022	Around 2–4 project
		PRIME	Max of 52 million yen total period for each project (including indirect costs)	Max. of 3.5 years FY2017–FY2020	Around 8–10 project
4	Studies on Specific Activities and Functions of Lipid Molecules to Develop Innovative Medical Technologies (Program Supervisor (PS): Shinji Yokoyama) (Program Officer (PO): Yasuyuki Igarashi)	AMED-CREST	Max of 390 million yen total period for each project (including indirect costs)	Max. of 5.5 years FY2017–FY2022	Around 2–4 project
		PRIME	Max of 52 million yen total period for each project (including indirect costs)	Max. of 3.5 years FY2017–FY2020	Around 8–10 project

- "Scale of R&D Funds" is an approximate estimate guide.
- "Scale of R&D Funds" and "Planned Number of New Awarded Projects" may change depending on the situation regarding budget appropriation following the commencement of applications. In the event that there is a significant change, it is possible that acceptance of applications submitted for some of all of the R&D projects being solicited or adoption of projects may be cancelled.
- Although applicants may submit applications for multiple R&D projects being solicited, in order to show that there is no unreasonable duplication or excessive concentration of competitive research funds (for details refer to Chapter V. 10 (4)), they must be sure to list information for all the other R&D projects for which applications are being submitted simultaneously in the relevant R&D Proposal column.

2. Preparation and Submission of R&D Proposals

(1) Methods for Obtaining Proposal Forms, Etc.

Please download forms for proposal documents and other materials necessary for application from the "Calls for Applications" page on the AMED website.

http://www.amed.go.jp/koubo/010720170310-01.html

(2) Period of Acceptance of Proposals

April 12, 2017 (Wed.) ~May 30, 2017 (Tue.) [12:00] (No exceptions)

Note 1: Procedures for registering with e-Rad can only be carried out during e-Rad system operating hours.
Note 2: For all R&D proposals, applications received after the deadline will not be accepted
Note 3: Registration requests will not be accepted after the deadline.

(3) Submission of Proposal Documents

Please submit proposal documents via e-Rad by the deadline. Applications will not be accepted if the proposal documents are not submitted by the deadline. When completing (inputting) the R&D proposal documents, please following the guidelines provided in this item and on the R&D Proposal (Form 1) and be sure that all the information you are required to provide is correct. Please note that submitted proposal documents cannot be replaced after the application deadline.

(a) Points to note in using the system

An e-Rad operating manual is available for reference or downloading from the e-Rad portal site (http://www.e-rad.go.jp/). Please read and agree to the system usage regulations before submitting your application.

1) System operating hours

The e-Rad system is available for use between 00:00 and 24:00 on weekdays and public holidays.

Note: During the above system operating hours, the e-Rad system by be temporarily shut down for maintenance or inspection. In the event that e-Rad is to be temporarily shut down, notice will be posted in advance on the e-Rad portal site.

2) Registration of research institute

In the case that researchers are applying for the program through a research institute, the "Principal Institution" (the research institute with which the PI is affiliated) and "Subsidiary Institution" (a research institute other than the Principal Institution with which a Co-Investigator is affiliated) must be registered with e-Rad prior to the time of application as a general rule.

For information regarding how to register research institutes, please refer to the e-Rad portal site. Registration procedures may require several days, so please allow leeway of two weeks or more for carrying out registration procedures. Please note that once you have registered with e-Rad, there is no need for you to register again for another R&D program or project. Moreover, if you have already registered with e-Rad for another R&D program or project, there is no need for you to register again. In the case that you are not affiliated with a specific research institute at the time of application or are affiliated with a research institute outside of Japan, please separately contact the department responsible for the relevant project as early as possible before submitting your application.

3) Registration of researcher information

The PI for the R&D project for which the application is to be submitted and the Co-Investigator participating in the research must register their researcher information and obtain a system login ID and password. The research institute should register information for researchers who are affiliated with it. Please note that researcher information registered previously for a scientific research grant is already registered in the e-Rad system. Please check your researcher number and input additional information regarding your affiliated research institution. Information for researchers who are affiliated with a research institute shall be registered by e-Rad system operation managers. Please refer to the e-Rad portal site for the necessary procedures.

(b) Points to note regarding submission of documents via the e-Rad system

1) Consent of affiliated institute

Application to the program is not complete at the point that the PI submits the application to their affiliated research institute via e-Rad. Make sure to undergo procedures to obtain approval of the R&D project from your affiliated research institute.

2) Downloading of proposal forms

Please download the prescribed form file after first checking the system/program information

3) File type

The electronic media format needs to be converted into PDF format before uploading. Please select PDF conversion from the menu that appears after you login. It is also possible to download conversion software from this menu and install it on your computer for your use. (In order to ease the burden on the system and realize stable operations, the option of submitting files in Word format, etc., as is, which was available under the old system, is no longer available.) If you use foreign-language letters or special characters, the text may be garbled, and so please be sure to check the content of the converted PDF file on the system. Please refer to the Researchers' Operation Manual with regard to letters/characters/symbols that may be used.

4) Image file format

Image files for insertion in proposal documents should be submitted in "GIF", "BMP", "JPEG", or "PNG" format. If image files in other formats (e.g. images created with different applications such as CAD, Scanner, PostScript, or DIP software) are inserted in the proposal documents, the documents cannot be converted to PDF format correctly. For information on how to insert image data into proposal documents, please refer to the Researchers' Operation Manual.

5) File capacity

The maximum capacity of files than can be uploaded is 5 MB.

6) Uploading proposal documents

Please convert proposal documents to PDF format before uploading.

7) Checking acceptance status

At the time of the deadline, if the acceptance status of your application shown on the system's "Application Acceptance Status Listing Screen" is not "Being processed by funding agency", the proposal documents are invalid. In the case that the message "Being processed by funding agency" does not appear by the application deadline, please contact your affiliated institute urgently. It is possible to check the acceptance status of proposal documents from the "Application Acceptance Status Listing Screen"

8) Amendment of proposal documents after submission

In order to amend proposal documents that have already been submitted, you need to carry out "Retrieval" procedures before the application deadline and then re-submit the amended documents. For details regarding retrieval procedures, please refer to the Researchers' Operation Manual.

9) "temporarily save" input information

It is possible to suspend input of and temporarily save application information part way through. For details, please refer to "Usage Manual for Researchers" or "Frequently Asked Questions" sections on the e-Rad portal site.

10) Other

Proposals containing incomplete or defective documents are excluded from the selection process. Read this Application Guidelines and the entry examples carefully and enter the required data (do not change the format of application documents.) Replacement of application documents is strictly prohibited. Submitted documents will not be returned.

In addition to those described above, notes and details are also provided in the e-Rad portal as required.

Details about points to note and content other than that shown above are posted as required on the e-Rad portal site (Researchers' Page), so please check this information.

(c) Contact for inquiries regarding e-Rad system operation

For inquiries regarding how to operate the e-Rad system, please contact the e-Rad portal site's Help Desk. (Please refer to Chapter X.) Please be sure to check the portal site and see the "Frequently Asked Questions" page before contacting the Help Desk. Please note that the Help Desk cannot answer any inquires whatsoever regarding the content of the Call for Applications, application review status, or acceptance/rejection of applications.

(4) Schedule for Review

The schedule from application to selection of projects for the program shown below is current as at the time that acceptance of applications begins. For details on how reviews are carried out, refer to Chapter III. 3.

Document review July 2017 (tentative)

Interview (hearing) Listed below (tentative)

Inteview schedule

R&D Area	AMED-CREST	PRIME
Clarification of the mechanism of individual functional impairment over the entire life course	August 6, 2017 (Sun.)	August 14, 2017 (Mon.) August 15, 2017 (Tue.)
Understanding the interactions and symbiosis between the microbiome and the host organism, leading to an understanding of the mechanisms of disease onset	August 9, 2017 (Wed.)	August 7, 2017 (Mon.) August 8, 2017 (Tue.)
Elucidation of Mechanobiological Mechanisms and Their Application to the Development of Innovative Medical Instruments and Technologies	August 10, 2017 (Thu.)	August 11, 2017 (Fri.) August 12, 2017 (Sat.)
Studies on Specific Activities and Functions of Lipid Molecules to Develop Innovative Medical Technologies	August 4, 2017 (Fri.)	August 5, 2017 (Sat.) August 6, 2017 (Sun.)

Note 1: In the case that a hearing is conducted, the PI for the relevant project shall as a general rule be contact by e-mail no later than one week before the hearing is to take place. (In the case that the project is not eligible for a hearing or hearings themselves are not being conducted, the PI will not be contacted. Please wait to receive your Notification of Selection/Rejection.) In the case that there is a change in information regarding the implementation or scheduling of hearings, this will be posted on the Application Information page on the AMED website listed in Chapter III.2. (1), so please refer to this page for details. Note that we cannot answer questions regarding the eligibility of individual projects for hearings.

Note 2: The PI of a project for which a hearing is to be conducted may be sent via e-mail a list of "Matters of Inquiry" that have arisen through the document review process. Please e-mail answers to these questions to the Secretariat by the deadline specified by AMED ahead of the hearing.

Note 3: As a general rule, the hearing shall be attended by the PI. The date and time of the hearing cannot be changed.

Note 4: Following the hearing, administrative matters may be confirmed with the PI as necessary. Please respond swiftly to the relevant checks via the method specified by AMED.

Notification of Selection/Rejection September 2017 (tentative)

Note: The PI of a project that has been selected as a candidate project for adoption may be required to revise the project's objectives, implementation plan, and/or implementation system in accordance with the review results, and conditions for adoption, including changes to the total R&D funding amount may be added. In such cases, the appropriateness of the plan may be reconsidered.

Commencement of R&D (Contracting, Etc.) (tentative date) October 1st, 2017 (Sun.)

Note: The "Tentative Date" has been set in consideration of the time period required for formulating an optimal R&D plan at the time of submitting the proposal with a view to the timing of the commencement of R&D, and to enabling researchers to make the preparations they can between the time of the decision to adopt the project and the time the contacted R&D agreement is concluded so that R&D can commence as swiftly as possible after conclusion of the agreement, and **does not guarantee conclusion of a contracted R&D agreement**. In order to conclude the contracted R&D agreement on the "Tentative Date", the cooperation and efforts of research institutes, etc. regarding the formulation and/or revision of R&D plans (including R&D funds and R&D systems) are required. AMED will also endeavor to coordinate with the PS/PO of a project as swiftly as possible to ensure that the contracted R&D agreement can be concluded as early as possible.

(5) Schedule for Briefing of Solicitation

Briefing of Solicitation **(NOTE: only in Japanese)** will be carried out below. The PS/PO will explain the operational outline and policy of each R&D area.

Date：April 28, 2017 (Fri.)
Place：Sola City Conference Center 2F, sola city hall【WEST】
4-6 Kanda Surugadai, Chiyoda-ku, Tokyo, 101-0062
Registration through AMED website is necessary (deadline: April 26 (Wed.) 18: 00)

Time	Contents
13：00～13：40	Explanation about general rules in the program
13：40～14：10	Elucidation of Mechanobiological Mechanisms and Their Application to the Development of Innovative Medical Instruments and Technologies (Program Supervisor (PS): Masahiro Sokabe) (Program Officer (PO): Joji Ando)
14：10～14：50	Clarification of the mechanism of individual functional impairment over the entire life course (Program Supervisor (PS):Eisuke Nishida) (Program Officer (PO):Eiji Hara)
15：00～15：40	Understanding the interactions and symbiosis between the microbiome and the host organism, leading to an understanding of the mechanisms of disease onset (Program Supervisor (PS): Chihiro Sasakawa) (Program Officer (PO): Hiroshi Ohno)
15：40～16：10	Studies on Specific Activities and Functions of Lipid Molecules to Develop Innovative Medical Technologies (Program Supervisor (PS): Shinji Yokoyama) (Program Officer (PO): Yasuyuki Igarashi)

Note1: The general explanation is only once from 13: 00 to 13: 40. Please note that the entire explanation will not be done in the time zone of explanation of each area.

Note2: It is possible to view videos freely after the briefings.

3. Method for Reviewing Proposal Documents

(1) Review Method

In selecting R&D projects under this program, ex-ante evaluations (reviews) shall be conducted by evaluators (reviewers) comprising external experts appointed by the President of AMED in order to determine the necessity of the R&D project, appropriateness of project objectives and plans, and budget allocation. The Project Evaluation Panel is composed of the PS, PO and R&D Area Advisers*. In addition, the cooperation of external evaluators may be requested. Selection recommendations are prepared by the PS for AMED-CREST and the PO for PRIME.

(a) Reviews shall be conducted in private by a Project Evaluation Panel established by AMED.

(b) The Project Evaluation Panel shall evaluate project proposals by conducting a document review of the content of the submitted proposal documents and conduct interviews (hearings) as necessary* and deliberating on the project content.

*During the review process, the PI may be required to provide additional materials, etc.

(c) In deciding projects for adoption, the PI of a project may be required to revise* the project's objectives, implementation plan, and/or implementation system in accordance with the review results, and conditions for adoption, including changes to the total R&D funding amount may be added. In such cases, the appropriateness of the plan may be reconsidered.

*In the case that the project is adopted, the objectives, etc., revised at this stage shall be used as evaluation indicators when interim and ex-post evaluations are carried out. Please refer to Chapter VI. for information regarding the management and evaluation of awarded projects.

(d) Following completion of reviews, AMED will send notification of selection/rejection to the PI of the project. Note that we cannot answer questions regarding the progress status of the selection process.

(e) Evaluation Panel members are obligated to maintain confidentiality regarding any secret information learned during the course of performing their evaluation duties, including after these duties have concluded, in order to prohibit leakage or misappropriation of this information. Furthermore, from the standpoint of conducting fair and transparent evaluations, interested parties must not be involved in the evaluation process.

(f) The names of the R&D projects adopted for the program (awarded projects) and the name of the PI will be published at a later date on the AMED website. Furthermore, as a general rule, the names of all evaluators (reviewers) shall be published by AMED once each year.

(g) From the standpoint of conducting fair and transparent evaluations, management of conflict of interest for Project Evaluation Panel members shall be implemented in accordance with AMED regulations. In the case that any of the following items apply to a Project Evaluation Panel member, they are required to report to AMED that they are subject to management of conflict of interest and as a general rule shall not be involved in evaluation of the relevant project. However, in the case that the Project Evaluation Panel Chair recognizes that participation by the Project Evaluation Panel member in question is especially necessary for ensuring the scientific validity of the evaluation and that their ability to make appropriate and transparent decisions as part of the evaluation is not impaired, the Project Evaluation Panel member may participate in the evaluation of the relevant project.

1) The evaluatee is a family member/relative of the Project Evaluation Panel member.
2) The evaluatee is affiliated with the same department at a university, the National Research and Development Agency, or a national research institution or other research institute or business enterprise as the Project Evaluation Panel member.
3) The evaluatee has worked closely with the evaluator on a joint research project within the past three years including the fiscal year in which the Project Evaluation Panel evaluation is conducted.
4) The Project Evaluation Panel member and evaluatee have a close teacher-disciple relationship wherein one provided guidance and instruction regarding the other's doctoral thesis.
5) The evaluatee has received economic benefits from the Project Evaluation Panel member within the past three years, including the fiscal year in which the Project Evaluation Panel evaluation is conducted, of more than one million yen.
6) The Project Evaluation Panel member is in a direct competitive relationship with the evaluatee.
7) Other serious conflicts of interest are recognized to exist.

(h) Program applicants and persons intending to apply for the program are prohibited from lobbying AMED executive officers, PD, PS, PO, or evaluators regarding evaluations or project selection.

(2) Review Criteria and Perspectives in Evaluating Projects

In selecting projects for this program, reviews of proposal documents shall be carried out from the following perspectives. In the case that a proposal is submitted for an R&D project that designates a subsidiary institution, evaluations shall also examine the necessity of the subsidiary institution for carrying out the R&D and the competency of the subsidiary institution to carry out the R&D.

(a) Compatibility with the program's purpose

・Is the project compatible with the program's purpose and objectives, etc.?
(Does the project contribute to the achievement of the aims of the R&D? In addition, it the project compatible with the aims of the R&D Area?)

(b) Scientific/technological significance and advantage

・Does the project proposal have originality, novelty, and innovativeness?
・Does the project respond to social needs?
・Is the project compatible with national policies regarding R&D in the field of medicine?
・Does the project contribute to the advancement of the field of medicine?

・Does the project contribute to the generation of new technologies?
・Is the current technological level and previous performance sufficient?
・In the case of AMED-CREST, is the basic research highly regarded internationally?
・Is the basic research in PRIME regarded challenging? Also, is the basic research in PRIME expected development at high level and internationally?

(c) Appropriateness of the plan

・Are the overall content and objectives of the plan clear?
・As the plans for each fiscal year detailed and realizable?
(Have milestones set appropriately in the plan? Also, does the applicant show promising preliminary results for realizing the R&D initiative?)
・Is the project plan in compliance with laws and ordinances related to bioethics or safety measures?

(d) Implementation system

・Has an R&D system centered on the applicant been organized appropriately?
・Has a sufficient collaboration network been constructed?
(Does the R&D Co-Investigator play an essential role in realizing the R&D initiatives? Has been the collaboration framework constructed sufficiently for enabling them to significantly contribute to achieving the R&D initiatives?)
・In the case of PRIME, is the proposed R&D project an appropriate scale for individual researchers to carry out?
・Are the efforts of the applicant appropriate?
・Do the participating or collaborating research institutions have R&D capabilities and other technological foundations in the relevant research field?
・Is there unreasonable duplication/excessive concentration?

(e) Costs

・Are the breakdown of costs and spending plan appropriate?
(Has R&D budget planning for realizing the Applicant's R&D initiatives been carried out appropriately?)

(f) Items prescribed under the program and items that should be considered comprehensively

・Is the applicant expected to contribute to the advancement of the overall R&D Area and the continuous development of related research fields through the proposed R&D project content, Research approaches and efforts such as discussion and mutual stimulation with other researchers?

Ⅳ. Preparation of Proposal Documents and Cautions

1. Handling of Information Contained in Proposal Documents

(1) Purpose of Use of Information

In addition to reviewing R&D project proposals as part of the selection proves, information included in proposal documents, etc., shall also be used by contracted R&D fund administration organizations and for research support purposes as described in IX.

Furthermore, information included in proposal summaries shall also be used in analysis of research trends that contributes to the operation of the AMED program, such as the creation of new programs. In accordance with laws related to the protection of personal information possessed by independent administrative corporations and other organizations, the confidentiality of secret information included in proposal documents shall be strictly maintained to ensure that the applicant is not disadvantaged unnecessarily. For details, please refer to the Ministry of Internal Affairs and Communications website.*

* "Introduction of legal systems for the protection of personal information by government organizations/independent administrative corporations, etc." (Ministry of Internal Affairs and Communications)
http://www.soumu.go.jp/main_sosiki/gyoukan/kanri/horei_kihon.html

(2) Necessary Disclosure/Provision of Information

(a) Information regarding individual awarded projects (name of program, name of R&D project, names of researchers, researchers' affiliated research institutes, budget amount, and implementation period) falls under "Information that is made public, or information that is scheduled to be made public, as provided for by law or by custom" as prescribed in Article 5 Paragraph (1) Item (a) of the Act on Access to Information Held by Independent Administrative Agencies, and therefore may be publicly disclosed. In addition, information necessary for macro analysis may be provided to the Cabinet Office via e-Rad for the purpose of inputting the information into the Government Research and Development Database (please refer to Chapter IX. 3.), and analysis results may be publicly disclosed.

(b) Within the scope necessary for eliminating unreasonable duplication/excessive concentration, some information included in proposal documents, etc., may be provided via e-Rad to divisions in charge of other competitive research funding programs, including other government ministries or agencies (including the provision of personal information used when computerized data processing and management is contracted out to an external private enterprise). Similarly, information may also be provided in the event that it is necessary to check for duplicate applications to other competitive research funding systems, etc.

2. Proposal Document Format and Notes for Preparation

(1) Proposal Document Format

All three types of documents will be needed for the application.

1. Summary of Proposal (in English)
2. Summary of Proposal (in Japanese)
3. R&D Proposal Forms (form No.1-13)

The proposal document form shall be the "R&D Proposal". Please complete each item simply and clearly. With regard to the acceptance period for proposal documents and submissions, please refer to Chapter III.

(2) Preparation of proposal documents

Applications are to be submitted via e-Rad. In preparing proposal documents, please also refer to the Points to Note shown in (3). If not completed correctly, proposal documents may not be accepted.

Please be careful with regard to the following items when inputting information onto the Proposal Form.

Form No.	Document	AMED-CREST	PRIME
1	R&D Proposal	○	○
2	R&D Proposal Overview	○	○

3	R&D Project Plan	○	○
4	Organization Chart	○	—
5	R&D Project Organization (R&D PI's Group)	○	○
6	R&D Project Organization (R&D Co-PI's Group)	○	—
7	Budget Plan	○	○
8	List of Achievements / Ex-Post Evaluation Results	○	○
9	List of Achievements (R&D Co-PI(s))	○	—
10	Patent List	○	○
11	Information on Other Supports	○	○
12	Ethical Considerations	○	○
13	References and Additional Statement	○	○

(a) As a general rule, the Research Proposal (Form 1) is to be prepared in Japanese, but the abstract must be prepared in both Japanese and English. In the case that information required on the Research Proposal is missing, the application may be ineligible for review.

(b) With regard to formats prescribing word limits or page limits, please be sure to comply with the set limits.

(c) With regard to letter/character size when inputting information, please use 10.5 point as a general rule.

(d) As a general rule, please use half-width letters when inputting English. (E.g. post codes, telephone numbers, numbers of people.)

(e) Please number the pages of proposal documents with numbers placed centrally at the bottom of each page in the form of (-1-).

(f) Proposal documents may be prepared in color, but please ensure that the documents' content can be understood even when the documents are photocopied in black-and-white.

(3) Notes on Preparing R&D Proposals

(a) Compliance with ministerial ordinances/ethical guidelines, etc.

In preparing R&D proposals, be sure to comply with relevant laws and ministerial ordinances/ethical guidelines prescribed by government ministries and agencies. For details, please refer to Chapter V. 4 (4).

(b) Approval of R&D Project Proposals by Organizations

In submitting proposal documents, the PI must obtain the approval of the head of the Principal Institution (research institute with which the PI is affiliated and which is to conclude a direct contracted agreement with AMED). Furthermore, in the case that multiple research institutes jointly submit an R&D proposal for carrying out research, the approval of the heads of all the research institutes must be obtained.

(c) Revision of R&D Proposal Content

In selecting R&D projects for adoption, due to budget restrictions and other reasons, it may be necessary to request applicants to revise their submitted research proposal plans. Furthermore, in implementing awarded R&D projects, please note that the expenditure/implementation period allocated to the project may need to be changed due to budget restrictions in the future.

(d) Ineligible Project Proposals

The following R&D projects are ineligible for funding under this program.

1) Proposals that aim simply to purchase ready-made equipment.
2) Proposals that envision covering the costs necessary for procuring equipment with funding from this program when covering these procurement costs with funding from another source would be appropriate.

(4) Required Documents Apart from R&D Proposals

(a) Records of ex-ante interviews/face-to-face advice with PMDA

In the case that the applicant has already undergone ex-ante interviews with PMDA under their "regulatory strategy consultation" program, a summary of the interview must be submitted with the R&D proposal (free format; summary may be provided by the academic institution), and if the applicant has already undergone face-to-face advice, a record of the face-to-face advice or separate sheet (consultation content) such be submitted with the R&D proposal.

Note: R&D projects that progress to the practical application stage (R&D projects within the scope of the "Regulatory strategy consultation" program) must as a general rule undergo face-to-face advice within one to two years of the project being adopted as a condition of the contracted R&D agreement (please refer to Chapter IV. 1. for details regarding the period in which the consultation should be undertaken). Although is it not compulsory for the applicant to have undergone face-to-face advice at the time of application, it is desirable that face-to face consultation is undertaken and the consultation results are reflected in the R&D plan.

(b) Materials related to clinical research, etc.

For research undertaking investigator-initiated trials or clinical trials with a view to creating innovative drugs or medical devices, or nonclinical studies aimed at conducting such trials,* applicants are required to submit materials related to the clinical research such as a trial plan and protocol (including information such as aims, subjects, selection criteria, exclusion criteria, number of cases, observation content, intervention content, statistical methods, and research system) (free format; a draft may be submitted if the trials/studies have not been implemented at the time of application).

*Note: Does not include clinical research that is not aimed at creating new drugs or medical devices or that differ from normal processes for evaluating/approving new medical technology.

(c) Self-monitoring/self-evaluation results related to animal experiments

With regard to research institutes conducting animal experiments using animal species specified under the Fundamental Guidelines for Proper Conduct of Animal Experiments and Related Activities in Academic Research Institutions (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) No. 71 of 2006) and Fundamental Guidelines for Proper Conduct of Animal Experiments and Related Activities in Implementing Agencies under the Ministry of Health, Labour and Welfare (Notification by Director, Health Science Division, Minister's Secretariat, Ministry of Health, Labour and Welfare on June 1, 2006), based on these fundamental guidelines, research institutes are required to submit a copy of the results of their most recently implemented self-monitoring/self-evaluation related to the research institute's conformance with these fundamental guidelines.

Ⅴ. Conclusion of Contracted R&D Agreements

1. Conclusion of Contracted R&D Agreements

(1) Agreement Conditions

With regard to awarded R&D projects, R&D projects a one-fiscal-year contracted R&D agreement shall be concluded between the head of the research institution implementing the R&D project* and the President of AMED in accordance with the principle of the accounting period of the national government. Successful applicants shall receive detailed information from AMED following project selection.

In concluding contracted R&D agreements, in the case that the conditions decided at the time the project was adopted have not been fulfilled based on the opinions of the Project Evaluation Panel, PS, and PO, etc., and agreement is not reached regarding both the content of the agreement (including expenditure estimates) and method, an agreement will not be concluded even for an awarded R&D project.

Even after the contracted R&D agreement has been concluded, in the case that unavoidable circumstances arise due to budget restrictions, the R&D project may need to be revised or suspended.

The PS or PO, etc., shall check on the R&D progress status, and the contracted R&D agreement may be changed or cancelled part-way through the fiscal year due to revisions to the R&D plan or other reasons.

*With regard to Principal Institutions and Subsidiary Institutions that are national facilities or other institutions (general term for national facilities or other institutions or public research institutes), only in the case that the relevant institution or the PI or Co-Investigator affiliated with the relevant institution makes a request based on reasonable grounds and following discussion with AMED shall a payment method of the R&D grant being paid By AMED to the PI or Co-Investigator of the relevant institution be adopted. (In such cases, payment will be in accordance with the Guidelines for Handling of R&D Grants prescribed by AMED.) If this is the case, administration related to R&D grant accounting shall be entrusted to the head of the relevant institution.

Furthermore, in the case that the need to carry out the research content at the Principal Institution and the Subsidiary Institution in an integrated manner under the R&D plan is recognized and the Subsidiary Institution is not a national facility or other institution, approval may be given under the program for the R&D to be subcontracted. However, even in the case that the R&D is subcontracted, as a general rule project accounting shall be performed by the subcontracted institution and the subcontracted institution shall be required to undergo auditing in response to requests from AMED.

(2) Preparations for Concluding Agreement

Following the adoption of an R&D project, the contracted institution shall be required to carry out the following to enable procedures for concluding the contracted R&D agreement to proceed quickly and smoothly.

(a) Preparation of an Overall R&D Plan and R&D Plan*

(b) Obtain an estimate for the expenditure needed under the administrative plan

(c) Organize accounting regulations rules for employee inventions, etc.

*One Overall R&D Plan is to be prepared for each R&D project based on the R&D proposal at the time of adoption of the project. Centered on the proposed R&D concept for the entire project implementation period, please include the basic plan, R&D content, R&D system, and budget plan. This plan shall be used as a base material for considering budget allocation each fiscal year, conducting interim and ex-post evaluations, and managing project progress.

One R&D Plan is to be prepared for each agreement when contracted R&D agreements for each fiscal year are concluded.

Plan forms shall be provided separately after projects have been adopted.

(3) Administrative Procedures Regarding Conclusion of Agreements

Please carry out the necessary administrative procedures based on the AMED "Administration Manual for Contracted R&D Agreement".*

*Link from: http://www.amed.go.jp/program/youshiki.html

(4) Determination of Contracted R&D Funding Amount

Contracted R&D funding amounts are determined based on examination of the Contracted R&D Accomplishments Report which is required to be submitted in accordance with the Contracted R&D Agreement following the conclusion of the Contracted R&D Agreement period for the relevant fiscal year. During this examination, in the case that expenditure for research purposes is found to have been used fraudulently or for

purposes not recognized as contracted R&D activities under the Contracted R&D Agreement, all or part of the expenditure may be required to be returned. Furthermore, the person(s) conducting the research who used the funds fraudulently may be excluded from any agreements with AMED for a certain period of time, depending on the extent of the fraud. (Please refer to V. 9. (2).)

2. Scope and Payment of Contracted R&D Funds

(1) Scope of Contracted R&D Funds

Under this program, items of expenditure have been set as follows. For details, please refer to the AMED "Administration Manual for Contracted R&D Agreement".[1]

Certain amount of an item of Direct Costs may be appropriated to another item of Direct Costs if such treatment is necessary for the performance of the Contracted Research and Development; provided, however, that the prior approval of AMED shall be obtained if the amount per item of such treatment exceeds fifty percent (50%) of Direct Costs (or five million yen (JPY 5,000,000), if an amount equal to fifty percent (50%) of Direct Costs is less than five million yen (JPY 5,000,000)).

	Main item	Definition
Direct costs	Costs of goods (equipment/supplies)	Research facilities/equipment/prototypes, software (ready-made goods), book purchasing costs, purchasing costs for reagents/materials/consumables for use in research
	Travel costs	Travel costs of R&D participants, travel costs for invited participants such as external experts
	Personnel costs[2]/ services costs	Personnel costs: personnel costs for researchers, etc., employed to conduct the relevant contracted R&D Service costs: expenditure for services such as lecture requests, guidance/advice, test subjects, interpreters/translators, and unskilled labor.
	Other	Costs for implementing the relevant contracted R&D other than the above. Examples: R&D results publication costs (academic paper contribution costs, academic paper offprint costs, website production costs, etc.), conference costs, equipment leasing costs, Equipment repair costs, printing costs, subcontract costs, testing costs, amount equivalent to consumption tax related to untaxed transactions, etc.
Indirect costs[3]	Expenditure used by research institutes and paid by AMED as necessary costs for managing the research institutes during implementation of the relevant R&D, paid at a fixed percentage of direct costs (within 30%) as an allowance.	

[1] Link from: http://www.amed.go.jp/program/youshiki.html

[2] In principle, personnel expense for PI and Co-PI cannot be paid from the direct costs of this program. However, in PRIME, please consult individually in the case that employment criteria of research institution defines to pay your own personnel cost from external fund(s) you have awarded.

[3] Implemented when AMED concludes a contracted R&D agreement with a national university corporation, inter-university research institute corporation, independent administrative corporation, special corporation, special private corporation, general incorporated association, general incorporated foundation, public interest incorporated association, public interest incorporated foundation, private enterprise, or private university, etc., and does not apply in the case that the researcher is affiliated with a national facility or other institution (excluding the National Institute for Educational Policy Research). With regard to Subsidiary Institutions (excluding national facilities or other institutions) also, indirect costs are allocated in accordance with direct costs.

(2) Appropriation of Contracted R&D Funds

Please calculate costs required for conducting the R&D and record the total amount. As a general rule, calculation and recording of costs should be performed in accordance with the AMED "Administration Manual for Contracted R&D Agreement".*

*Link from: http://www.amed.go.jp/program/youshiki.html

Note: Contracted R&D agreements for researcher-initiated trials or clinical studies under AMED shall in future incorporate "Contract management method using value per procedure (VPP) charts in researcher-initiated trials or clinical studies".* In the case that an awarded R&D project is recognized as being subject to this management method, if the research institute has created a system for registering cases for trials/clinical research in accordance with newly prescribed internal consignment regulations ("Regulations for Handling Contracted R&D in Researcher-initiated Trials and Clinical Trials" (tentative title), the head of the research institute can request case registration from other medical institutions in a kind of outsourcing method. For details, please refer to AMED "Operation of Research Funds: Management of Medical Institution Expenditure for Researcher-initiated Trials and Clinical Trials" (link from: http://www.amed.go.jp/program/kenkyu_unyo.html).

*Facilities where there is a sufficient administrative support system for trials/clinical research may continue using their current management method for the foreseeable future.

(3) Payment of Contracted R&D Funds

As a general rule payment of contracted R&D funds shall be made each quarter in even (one-quarter) installments of the total amount for direct and indirect costs for the entire fiscal year.

(4) Provision of Documentary Evidence (Receipts, Etc.) for Indirect Costs

The research institution which receives indirect costs should manage these costs properly and keep receipts and other documents confirming the proper use of indirect costs for five years from the next fiscal year of that in which the project is completed. The head of the contract institution which receives indirect costs must submit a report for the expenditure record of indirect costs every fiscal year. Details should be confirmed with the AMED Contract Research and Development Agreement Administration Manual*".

*Link from: http://www.amed.go.jp/program/youshiki.html

3. Carryover of Contracted R&D Funds

In the course of the program, in the case that it becomes difficult to ensure completion of contracted R&D fund payments within the relevant fiscal year due to difficulty deciding preliminary surveys or research methods for the R&D, various conditions related to the R&D plan, weather-related issues, difficulty in procuring materials, or other unavoidable reasons, the contracted R&D funds may be carried-over to the end of the next fiscal year maximum with the approval of the Minister of Finance.

For details, please refer to the AMED "Administration Manual for Contracted R&D Agreement".

*Link from: http://www.amed.go.jp/program/youshiki.html

4. Obligations of Research Institutes in Implementing this Program

(1) Compliance with Laws and Ordinances

In implementing this program, research institutes must be observant of the fact that their research is being funded with public funds and strictly comply with related national government laws and ordinances, endeavoring to ensure that the program is implemented fairly and efficiently. In particular, research institutes shall be required to take measures to prevent misconduct[1], fraudulent use[2], and fraudulent receipt[3] (hereinafter referred to collectively as "Misconduct, etc.").

[1]"Misconduct" refers to the fabrication, falsification, or plagiarism of data or survey results, etc. included in research accomplishments published through submission to a journal, etc. (hereinafter referred to as an "Academic paper, etc.") by a researcher, either willfully or through gross negligence of the fundamental duty of diligence that researchers bear in carrying out their research activities. The definitions of each of the above terms is as follows.

(i) Fabrication: creation of data or research accomplishments that do not exist.

(ii) Falsification: manipulation of research materials, equipment, or processes and changing results obtained from data or research activities to results that are untrue.

(iii) Plagiarism: appropriation of the ideas, analysis methods, data, research accomplishments, academic papers, or terminology of another researcher without the approval of the relevant researcher or appropriate acknowledgement.

[2]"Fraudulent use" refers to the use of public R&D funds, either willfully or through gross negligence, for a purpose other than that for which it was intended, or in a manner that infringes the content of the grant decision or conditions for use of the public R&D funds (including, but not limited to, purposes or uses other than those stated in the R&D plan, or use of R&D funds that infringes laws, ordinances, regulations, notifications, or guidelines, etc.)

[3]"Fraudulent receipt" refers to a researchers receiving public R&D funds through falsehoods or other unfair means.

*Under the above definitions, "researcher" refers to a researcher, technician, research assistant, or other person conducting research activities using public R&D funds, or a person engaged in work subsidiary to these research activities.

(2) Participation in/Completion of Research Ethics Education Program

As part of measures to prevent misconduct from occurring, AMED requires all researchers participating in this program to take and complete a research ethics education program. Research institutes shall implement research ethics education for researchers and report to AMED on the status of participation. (For details, please refer to Chapter V. 7. and the AMED website.)

Furthermore, in the case that a researcher does not fulfill their obligation to undergo the prescribed research ethics education despite AMED's urging, the research institute may be directed by AMED to suspend all or part of the contracted R&D funding. In this case, research institutes must suspend contracted R&D funding as directed by AMED and not recommence funding until directed to do so.

(3) Conflict of Interest Management

In order to ensure the fairness and reliability of research, in accordance with AMED's "Regulations for Managing COI in Research Activities" (March 17, 2016; Regulation No. 35 of 2016), the situation regarding conflict of interest for researchers involved in R&D projects shall be managed appropriately and reported.

In the case of research institutes conducting R&D under the AMED program, in the case that AMED determines that the conflict of interest of the PI or Co-Investigator of a project is not being managed appropriately, AMED may instruct the research institute to improve the situation or suspend provision of R&D funds, as well as require the research institute to return all or part of the R&D funds already paid. For details, please refer to the AMED website.

(4) Compliance with Laws/Ordinances and Ethical Guidelines

In the case that implementation of the proposed R&D concept involves research requiring procedures based on laws/ordinances and/or ethical guidelines (such as R&D requiring the consent/cooperation of another party; R&D requiring care in handling personal information; and R&D requiring measures regarding bioethics/safety measures), research institutions must undertake the necessary procedures for obtaining the approval of both internal and external ethics committees.

Please note that, in the case that R&D is carried out in infringement of related laws/ordinances and policies that must be complied with, the R&D may be suspended, the contracted R&D agreement cancelled, and/or the decision to adopt the R&D project cancelled.

Furthermore, in the case that the R&D plan includes R&D or surveys requiring the consent/cooperation of another party or social consensus, research institutes must take appropriate measures with regard to the handling of preservation of human rights and interests.

Within 61 days after the end of each fiscal year or the conclusion of the contracted R&D project, research institutions shall report to AMED regarding the status of ethical reviews by research institutes concerning related laws/ordinances and policies, as well as the status of conflict of interest management.

With regard to R&D related to life sciences in particular, the main laws and ordinances prescribed by government ministries and agencies are as follows. In addition, there are also laws and ordinances that pertain to certain R&D content, so please check the latest revision of laws/ordinances, etc.

- Act on Regulation of Human Cloning Techniques (Act No. 146 of 2000)
- Act on Prevention of Infectious Diseases and Medical Care for Patients Suffering from Infectious Diseases (Act No. 106 of 2006)
- Law Concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Law No. 97 of 2003)
- Act on the Safety of Regenerative Medicine (Act No. 85 of 2013)
- Guidelines on the Handling of Specified Embryos (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) No. 173)
- Guidelines on the Derivation of Human Embryonic Stem Cells (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and the Ministry of Health, Labour and Welfare (MHLW) No. 2 of 2014)
- Guidelines on the Distribution and Utilization of Human Embryonic Stem Cells (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) No. 174 of 2014)
- Guidelines on the Research on Producing Germ Cells from Human iPS Cells or Human Tissue Stem Cells (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) No. 88 of 2010)

- Ethical Guidelines for Human Genome/Gene Analysis Research (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) , the Ministry of Health, Labour and Welfare (MHLW) and the Ministry of Economy, Trade and Industry (METI) No. 1 of 2013)
- Ministerial Ordinance on Good Clinical Practice for Drugs (Ordinance of the Ministry of Health and Welfare No. 28 of March 27, 1997)
- Ministerial Ordinance on Good Clinical Practice for Medical Devices (Ordinance of the Ministry of Health, Labour and Welfare (MHLW) No. 36 of 2005)
- Ministerial Ordinance on Good Clinical Practice for Regenerative Medical Products (Ordinance of the Ministry of Health, Labour and Welfare (MHLW) No. 89 of 2014)
- Ministerial Ordinance on Good Laboratory Practice for Nonclinical Safety Studies of Drugs (Ordinance of the Ministry of Health, Labour and Welfare (MHLW) No.21 of 1997)
- Ministerial Ordinance on Good Laboratory Practice for Nonclinical Safety Studies of Medical Devices (Ordinance of the Ministry of Health, Labour and Welfare (MHLW) No.37 of 2005)
- Ministerial Ordinance on Good Laboratory Practice for Nonclinical Safety Studies of Regenerative Medical Products (Ordinance of the Ministry of Health, Labour and Welfare (MHLW) No.88 of 2014)
- On the Approach of Research and Development Using Human Tissues Obtained from Surgery (Report of the Health Science Council, the Ministry of Health and Welfare, 1998)
- Ethical Guidelines for Medical and Health Research Involving Human Subjects (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology (MEXT), and Ministry of Health, Labour and Welfare (MHLW) No. 3 of 2014)
- Policies on Clinical Research Involving Gene Therapy (Public Notice of the Ministry of Health, Labour and Welfare (MHLW) No. 344 of 2015)
- Ethical Guidelines for Assisted Reproductive Technology Studies Involving Production of Human Fertilized Embryos (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and the Ministry of Health, Labour and Welfare (MHLW) No. 2 of 2010)
- Fundamental Guidelines for Proper Conduct of Animal Experiments and Related Activities in Academic Research Institutions (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) No. 71 of 2006); Fundamental Guidelines for Proper Conduct of Animal Experiments and Related Activities in Implementing Agencies under the Ministry of Health, Labour and Welfare (Notification by Director, Health Science Division, Minister's Secretariat, Ministry of Health, Labour and Welfare (MHLW) on June 1, 2006; partially revised on February 20, 2015); and Fundamental Guidelines for Proper Conduct of Animal Experiments and Related Activities in Implementing Agencies under the Ministry of Agriculture, Forestry and Fisheries (Notification by the Director-General of the Secretariat, Agriculture, Forestry and Fisheries Research Council, Ministry of Agriculture, Forestry and Fisheries (MAFF) on June 1, 2006)

*Please refer to the following websites for details regarding bioethics and ensuring safety.
・MEXT's Life Sciences Forum "Initiative on Bioethics and Biosafety"
http://www.lifescience.mext.go.jp/bioethics/index.html
・Regarding Guidelines on Research (Ministry of Health, Labour and Welfare (MHLW))
http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/hokabunya/kenkyujigyou/i-kenkyu/index.html

(5) Management Responsibility for Executing Contracted R&D Funds

The entire amount of contracted R&D funds shall be executed by the research institute in accordance with the contracted R&D agreement. For this reason, research institutes shall abide by the principles stipulated under "Competitive research funding should be managed at the responsibility of the research institution" in the Guidelines for Management and Audit of Public Research Funds at Research Institutions (implementation standards)* (decided by Director, Health Science Division, Minister's Secretariat, Ministry of Health, Labour and Welfare (MHLW) on March 31, 2014), and research funds shall be managed under the responsibility of research institutes in accordance with "Items required to be implemented by institutions" as prescribed in the above guidelines.

5. Response Obligations Regarding System Maintenance and Submission of Self-evaluation (Including System Maintenance) Checklist

(a) Obligation to take action with regard to system maintenance

All research institutes must strictly comply with the items required to be implemented by research institutes (including establishing systems related to the management/auditing of public research funds) in accordance with the Guidelines for Responding to Misconduct in Research Activities (decided by the Minister of Education, Culture, Sports, Science and Technology on August 26, 2014) and the Guidelines for Management and Audit of Public Research Funds at Research Institutions (implementation standards)" (decided by the Minister of Education, Culture, Sports, Science and Technology on February 15, 2007; revised on February 18, 2014)

(b) Confirmation of system maintenance

Under the contracted R&D agreement for this program, research institutes may be requested to report the implementation status of system maintenance concerning the management and monitoring of public research funds to the MEXT using a Self-evaluation (Including System Maintenance) Checklist (hereinafter referred to as "Checklist"), as well as conduct various surveys regarding system improvement, etc.

For this reason, all research institutes must submit a checklist based on the format provided on the website shown below to the MEXT via e-Rad by a deadline to be stipulated separately by AMED.

http://www.mext.go.jp/a_menu/kansa/houkoku/1324571.htm

(c) Necessity of submitting checklists

In the case that you have already submitted a checklist this fiscal year when applying for a MEXT program, it is not necessary to newly submit a checklist when applying for another the MEXT program or concluding a contracted R&D agreement in the same fiscal year.

Under public research funding management and monitoring guidelines, it is required that a checklist be submitted around once each fiscal year, and so research institutes that are continuing implementation in the following year and beyond must also submit a checklist to the MEXT once each fiscal year.

*Registration with e-Rad

In order to submit a checklist, it is essential to create an environment that enables use of e-Rad, and so research institutes that have not yet implemented e-Rad registration procedures should do so immediately. Please note that registration usually takes around two weeks to complete.

For details regarding registration procedures, please refer to the "Preliminary Preparations for Using the System" section on the following websites provided for research institutes affiliated with e-Rad.

http://www.e-rad.go.jp/shozoku/system/index.html

http://www.mext.go.jp/a_menu/kansa/houkoku/1324571.htm

http://www.mext.go.jp/a_menu/kansa/houkoku/1301688.htm

(d) Cooperation with surveys

After submitting the checklist, research institutes may be requested to cooperate as necessary in surveys related to system improvement status conducted by the MEXT.

(e) Issue of conditions for managing public research funds and measures for reducing indirect costs

In the case that it is determined based on reports/surveys of public research funding management/monitoring system improvement that a research institute's system improvement is inadequate shall be issued management conditions by the MEXT in accordance with the Guidelines for Management and Audit of Public Research Funds at Research Institutions (implementation standards)" (decided by the Minister of Education, Culture, Sports, Science and Technology on February 15, 2007; revised on February 18, 2014) stating the items requiring improvement and the deadline for implementing these improvements (one year).

Please note that, in the case that it is subsequently deemed that the research institution has not fulfilled these conditions, AMED shall implement measures against the research institute such as reducing indirect costs with regard to R&D funding and/or suspending allocation of competitive research funding.

*Please refer to the following website.

Guidelines for Management and Audit of Public Research Funds at Research Institutions (implementation standards)" (decided by the Minister of Education, Culture, Sports, Science and Technology on February 15, 2007; revised on February 18, 2014)

http://www.mext.go.jp/component/a_menu/science/detail/__icsFiles/afieldfile/2014/03/18/1343906_02.pdf

6. Obligations of Researchers Participating in Research Activities under this Program

(1) Fair and Appropriate Execution of Contracted R&D Funds

Researchers participating in research activities under this program should be fully aware of the fact that AMED contracted R&D funds are provided by precious tax paid by the general public, and are obligated to execute funds fairly, appropriately, and efficiently.

(2) Application Procedures

When lodging an application for this program, the researcher who is to be responsible for R&D must make the appropriate arrangements, such as explaining the research to and receiving approval for the research from the research institute that is to conduct the R&D project in advance.

(3) Participation in/Completion of Research Ethics Education Program

In order to prevent fraudulent use, fraudulent receipt, and misconduct, researchers participating in this program are required to complete a research ethics education program. Please note that in the case that a researcher does not complete a research ethics education program, execution of contracted R&D funds may be suspended until completion of the research ethics education program is confirmed.

7. Participation in Research Ethics Program

(1) Program(s) to be Undertaken/Educational Materials

Persons required to undergo research ethics training as listed in (2) below shall undergo training using one of the following programs/materials.

- CITI Japan e-Learning Program
- "For the Sound Development of Science: The Attitude of a Conscientious Scientist" (Japan Society for the Promotion of Science Editing Committee "For the Sound Development of Science")
- Programs implemented by research institutes whose content is deemed to be equivalent to the that of the above programs

(2) Persons Required to Undergo Research Ethics Training

Persons required to undergo research ethics training shall be researchers whom research institutes (included subcontracted institutions by principal insitution) determine to be participating substantially in research activities being conducted with research funds provided by AMED.

(3) Research Ethics Training Period

As a general rule, persons required to undergo research ethics training shall undertake this training within the first fiscal year of the R&D period, and should continue to undertake ethics training as appropriate thereafter. (Training undertaken previously may also be valid.)

(4) Role of Research Institutes

Research institutes shall ensure that persons required to undergo research ethics training as listed in (2) above who are affiliated with their institution (included a subcontracted institution by principal insitution) undergo the R&D ethics education using one of the programs/materials listed in (1) above, and shall report on their training status to AMED.

(5) Reporting Research Ethics Training Status

Research institutes shall compile information on researchers' R&D ethics education status and submit a report on the status of training on the form prescribed by AMED by e-mail to AMED (Department of Research Integrity and Legal Affairs). (Seal need not be affixed.)

Subject of report: Persons required to undergo research ethics training in programs commencing in/after FY2016
Deadline for submission: End of May of the year following training
Documents to be submitted: "Report on the Status of Participation in R&D Ethics Education Programs" (Please download the form from the AMED website)
URL: http://www.amed.go.jp/kenkyu_kousei/

Where/how to submit report: Please e-mail the report to kenkyuukousei“at”amed.go.jp
(Change “at” to @ when inputting the address.)
Subject line: “FY2017 R&D Ethics Education Status Report XXX” (Replace XXX with the name of the research institute.)

(6) Inquiries

For inquiries related to R&D ethics education programs, please send an e-mail to [kenkyuukousei“at”amed.go.jp] (Change “at” to @ when inputting the address.)

8. COI Management

(1) Target Programs/Projects

(a) All R&D projects commencing in or after FY2016

- Excludes all activities unrelated to R&D (infrastructure improvement, human resources training, etc.)
- Research institutes that have not completed preparation of conflict of interest regulations or a conflict of interest committee as at April 2016 shall be exempted from application of AMED Regulations for Managing COI in Research Activities until March 31, 2018. However, such research institutes must also endeavor to implement appropriate management of conflict of interest regarding researchers participating in AMED programs.

(b) R&D projects commencing in or before FY2015 that are projects under programs listed in the appendix of the regulations

- However, such projects commencing in or before FY2015 under programs other than those listed in the appendix of the regulations must also endeavor to implement appropriate management of conflict of interest regarding researchers participating in AMED programs.

(2) Target Persons

PI or Co-Investigator of R&D projects

(3) Requests for COI Reviews

Prior to the conclusion of a contracted R&D agreement for the relevant R&D project each fiscal year, target persons shall report to the COI Committee regarding matters related to economic interests and then comment regarding reviews concerning conflict of interest in the R&D project.

(4) Submission of Ethics Review and COI Status Reports

The PI and Co-investigator affiliated with each research institute shall prepare an ethics review and conflict of interest status report for each project in which they are involved; have the head of the affiliated research institute affix his/her seal to the documents, and then submit the documents to the program department responsible for the relevant project by postal mail. (The research institute should also compile and submit a report by the Co-Investigator at contracted institutions.) The deadline for submission of reports is within 61 days after the end of each fiscal year or the conclusion of the contracted R&D project.

(5) Inquiries

For inquiries related to conflict of interest management, please send an e-mail to [kenkyuukousei“at”amed.go.jp] (Change “at” to @ when inputting the address.)

*For details, please refer to the following websites
- Regulations for Managing COI in Research Activities
  http://www.amed.go.jp/content/files/jp/kenkyukousei/riekisohan_kisoku.pdf
- Regulations Q&A
  http://www.amed.go.jp/content/files/jp/kenkyukousei/riekisohan_kisoku-qa.pdf
- Reports on the State of Ethical Reviews and COI Management
  http://www.amed.go.jp/content/files/jp/kenkyukousei/riekisohan_houkokuyoshiki.docx

9. Countermeasures to Misconduct, Fraudulent Use, and Fraudulent Receipt

(1) Reporting of and Cooperation in Investigations of Misconduct, Fraudulent Use, and Fraudulent Receipt Related to this Program

In the case that a complaint (including criticism from external organizations such as the media or the Board of Audit) related to misconduct, fraudulent use, or fraudulent receipt (hereinafter collectively referred to as "misconduct") by a research institute in relation to this program, the research institute shall swiftly report to AMED that it will be commencing a preliminary investigation into the matter in accordance with the Guidelines for Responding to Misconduct in Research Activities (decided by the MEXT on August 26, 2014); Guidelines for Management and Audit of Public Research Funds at Research Institutions (implementation standards)" (decided by MEXT on February 15, 2007; revised on February 18, 2014); and AMED Regulations for Responding to Misconduct in Research Activities (formulated on April 1, 2015; revised on February 19, 2016; Regulation No. 34 of 2016).

In the event that it is deemed necessary for the research institute to conduct such an investigation, an investigative committee must be established and the policy, targets, and methods of the investigation discussed with AMED.

Note that in this case, AMED may order the complainee and/or the research institute to suspend use of research funds under this program as a temporary measure during the investigation if necessary.

Furthermore, the research institute must submit to AMED a final report including the investigation outcome, cause of the misconduct, status of management/auditing of other competitive research funding in which the people involved in the misconduct are also involved, and plan for preventing recurrence by the deadline prescribed under the AMED Regulations for Responding to Misconduct in Research Activities (formulated on April 1, 2015; revised on February 19, 2016; Regulation No. 34 of 2016).

In the case that it is confirmed that misconduct has occurred even partially and even before the investigation has been completed, the research institute must swiftly recognize this fact and report it to AMED, as well as submit an investigation progress report and/or interim investigation report, even if the investigation has not yet concluded.

Please note that, except in the case that there is a legitimate reason, such as hindering the investigation, the research institute must submit materials pertaining to the relevant case to AMED and respond to AMED's perusal of these materials and on-site investigations.

In the case that that research institute extends the deadline for submission of the final report, AMED may take measures against the research institute such as reducing indirect costs by a certain percentage or suspending execution of contracted R&D funds. In addition, for details regarding items that should be incorporated into the final report, please refer to Guidelines for Responding to Misconduct in Research Activities (decided by the MEXT on August 26, 2014); Guidelines for Management and Audit of Public Research Funds at Research Institutions (implementation standards)" (decided by MEXT on February 15, 2007; revised on February 18, 2014); and AMED Regulations for Responding to Misconduct in Research Activities (formulated on April 1, 2015; revised on February 19, 2016; Regulation No. 34 of 2016).

(2) In the Event that Misconduct, Fraudulent Use, or Fraudulent Receipt is Discovered

In the case that misconduct takes place under this program, the following measures will be taken against the relevant research institute and researcher(s) in accordance with Guidelines for Responding to Misconduct in Research Activities (decided by the MEXT on August 26, 2014); Guidelines for Management and Audit of Public Research Funds at Research Institutions (implementation standards)" (decided by MEXT on February 15, 2007; revised on February 18, 2014); and AMED Regulations for Responding to Misconduct in Research Activities (formulated on April 1, 2015; revised on February 19, 2016; Regulation No. 34 of 2016).

(a) Cancellation of contracted R&D agreement

In the case that AMED recognizes that misconduct has taken place under this program, AMED shall cancel the contracted R&D agreement with the relevant research institute and demand the return of all or part of the contracted R&D funds from the research institute. Furthermore, AMED may not provide contracted R&D funds to the relevant research institute for the next fiscal year or thereafter.

(b) Restrictions on applications and participation

Researchers who are found to have carried out misconduct under this program or who are recognized as having been involved in or responsible for the misconduct shall have their application to and participation in AMED programs restricted in accordance with the degree of misconduct as shown in the table below.

[In the case of misconduct]

*The period of restriction deemed appropriate in consideration of the category of misconduct according to the person's involvement in the misconduct, between one year and ten years from the fiscal year in which the day the misconduct is recognized occurs or the next fiscal year.

<table>
<tr><th colspan="3">Category of misconduct according to involvement</th><th>Degree of misconduct</th><th>Period deemed appropriate</th></tr>
<tr><td rowspan="5">Person Involved in the Misconduct</td><td colspan="2">1. Especially malicious individual who intentionally engages in misconduct from the outset of the research</td><td></td><td>10 years</td></tr>
<tr><td rowspan="3">2. Author of academic paper, etc. related to research in which there has been misconduct</td><td rowspan="2">The author responsible for the academic paper in question (supervisor, first author, or other position of responsibility deemed equivalent)</td><td>The impact on the advancement of research in the relevant field or society is large, and the maliciousness of the misconduct is deemed to be high.</td><td>5–7 years</td></tr>
<tr><td>The impact on the advancement of research in the relevant field or society is small, and the maliciousness of the misconduct is deemed to be low.</td><td>3–5 years</td></tr>
<tr><td>Author other than that listed above</td><td></td><td>2–3 years</td></tr>
<tr><td colspan="2">3. An individual involved in misconduct other than that stipulated in 1 or 2</td><td></td><td>2–3 years</td></tr>
<tr><td colspan="3" rowspan="2">An author responsible for academic papers, etc. related to research in which there has been misconduct but who was not involved in the misconduct (supervisor, first author, or other position of responsibility deemed equivalent)</td><td>The impact on the advancement of research in the relevant field or society is large, and the maliciousness of the misconduct is deemed to be high.</td><td>2–3 years</td></tr>
<tr><td>The impact on the advancement of research in the relevant field or society is small, and the maliciousness of the misconduct is deemed to be low.</td><td>1–2 years</td></tr>
</table>

[In the case of fraudulent use/fraudulent receipt]

*The period of restriction deemed appropriate in consideration of the content of the fraudulent use/fraudulent receipt, between one year and ten years from the fiscal year in which the day on which execution of the research funds is suspended or the next fiscal year.

Content of usage of research funds	Period deemed appropriate
1. The degree of fraudulent use of research funds is deemed to have a small social impact and be slightly pernicious	1 year
2. The degree of fraudulent use of research funds is deemed to have a large social impact and be highly slightly pernicious	5 years

3. Cases other than 1 or 2 that are deemed to have a social impact or be pernicious	2–4 years
4. Cases in which research funds were used for personal economic gain, regardless of 1 through 3	10 years
5. Cases in which the relevant project was adopted as an R&D project through falsehoods or other dishonest means	5 years
6. Cases in which the person is not directly involved in fraudulent use of research funds but uses the research funds in a manner that infringes duty of diligence	1–2 years

**In the following cases, the offender shall be given a reprimand without imposing restrictions on application.

- In 1–4, the person's actions are deemed to have a small social impact and be slightly pernicious, and the funding amount used fraudulently is small.
- In 6, researchers whose actions are deemed to have a small social impact and be slightly pernicious, and who neglected duty of diligence.

Furthermore, in the case that misconduct is recognized to have taken place under this program and restrictions are place on the researcher's application to and participation in AMED programs, the researcher's application to and participation in research funding programs provided by related government ministries/agencies may similarly be restricted as information regarding the misconduct shall be provided to those in charge of programs under which competitive research funds are allocated by related government ministries/agencies or independent administrative corporations under the jurisdiction of related government ministries/agencies.

(c) Restrictions on researchers whose application to and participation in other R&D funding programs has been restricted

With regard to researchers who have been found to have carried out misconduct under R&D funding programs other than this program that are under the jurisdiction of the national government or an independent administrative corporation and are government-financed either wholly or in part, and whose application to and participation in these programs has been restricted, application to and participation in this program shall also be restricted for the duration of the restrictions imposed. In the case that the relevant researcher's application to or participation in this program becomes known after adoption by another program, adoption by the relevant program may be cancelled. Furthermore, in the case that the relevant researcher's participation in the program becomes known after the conclusion of the contracted R&D agreement, the relevant agreement may be cancelled.

(d) Cases in which it is suspected that misconduct has occurred under another R&D funding program

In the case that there is a complaint, etc., that a researcher participating in this program is suspected of perpetrating misconduct under another R&D funding program, the research institute with which the relevant researcher is affiliated is obligated to report to AMED that an investigation of the relevant misconduct allegations has been implemented.

Please note that, on receipt of this report, AMED may order the temporary suspension of usage of contracted R&D funds if deemed necessary.

Furthermore, in the case that the research institute to which the relevant researcher is affiliated fails to make the above report, the contracted R&D agreement may be cancelled.

(e) Disclosure of misconduct

In the case that the measures and/or restrictions prescribed in 1) and 2) above are implemented under this program, the content of the relevant measures shall be publicly disclosed in accordance with Guidelines for Responding to Misconduct in Research Activities (decided by the MEXT on August 26, 2014); Guidelines for Management and Audit of Public Research Funds at Research Institutions (implementation standards)" (decided by MEXT on February 15, 2007; revised on February 18, 2014); and AMED Regulations for Responding to Misconduct in Research Activities (formulated on April 1, 2015; revised on February 19, 2016; Regulation No. 34 of 2016).

(3) Admission to the AMED RIO Network

AMED plans to construct a network called the "RIO Network"* in FY2017. Research institutes that have concluded contracts with AMED shall register the officers in charge of R&D ethics education, the officers in charge of promoting compliance, and the officers in charge of administrative activities related to R&D misconduct and research funding misconduct with AMED and participate in RIO Network activities.

*A network comprising Research Integrity Officers (RIO) (officers in charge of R&D ethics education and officers in charge of promoting compliance) and officers responsible for related administrative activities for research institutes conducting R&D with AMED funds.

10. Points to Note between Selection and Conclusion of Agreement

(1) Cancellation of Decision to Adopt R&D Project

Following adoption of the R&D project, the decision to adopt the R&D project may be cancelled in the following cases.

- Documents required by AMED to be submitted are not submitted by the submission deadline
- A researcher/researchers involved in the relevant R&D have had their application to/participation in AMED R&D programs restricted
- An investigation has been opened into allegations of misconduct

(2) Researchers Undergoing Investigation/Researchers Discovered to Have Undertaken Misconduct

Please note that in concluding contracted R&D agreements, AMED requires research institutes to provide representation and warranty with regard to items (a) through (c) below.

(a) The "PI" or person in an equivalent position (as the person in charge of the R&D for the project), and the "Co-Investigator" or person in an equivalent position (as the person sharing R&D items with the PI for the project) have not been found by the research institute to have carried out misconduct in accordance with Japanese Government guidelines for responding to misconduct* (excluding, however, persons who have not has restrictions on application to/participation in competitive research funding programs implemented by the national government or independent administrative corporations based on the findings of the research institute, or whose period of restriction on application to/participation in competitive research funding programs implemented by the national government or independent administrative corporations has ended).

(b) In the case that persons who are the subject of an investigation (hereinafter referred to as the "Investigation") being conducted by the research institute in accordance with Japanese Government guidelines for responding to misconduct are either the PI or Co-Investigator for the R&D Plan, AMED has been notified of the relevant target persons by the day before the contracted R&D agreement was concluded and AMED's consent has been obtained with regard to handling of the relevant target persons.

(c) The research institute is strictly complying with and implementing each of the items that research institutes are required to implement as research institute system improvements as prescribed under Japanese Government guidelines for responding to misconduct.

*In the case that a research institute with which AMED has concluded a contracted R&D agreement also concludes a contracted agreement with a third party (from AMED's perspective, a subcontracted agreement. Hereinafter, the third party shall be referred to as the "Subcontractor"), please note that of the researchers affiliated with the Subcontractor, the relevant research institute is also required to provide representation and warranty for the "Co-Investigator" (or person in an equivalent position).

*The "Japanese Government guidelines for responding to misconduct" referred to in this item are the following guidelines.

- Guidelines for Responding to Misconduct in Research Activities in the Field of Health, Labour and Welfare (No. 0116-1, decided by Director, Health Science Division, Minister's Secretariat, Ministry of Health, Labour and Welfare (MHLW) on January 16, 2015)
- Guidelines for Management and Audit of Public Research Funds at Research Institutions (implementation standards) (decided by Director, Health Science Division, Minister's Secretariat, Ministry of Health, Labour and Welfare (MHLW) on March 31, 2014)
- Guidelines for Responding to Misconduct in Research Activities (decided by the Minister of Education, Culture, Sports, Science and Technology on August 26, 2014)
- Guidelines for Management and Audit of Public Research Funds at Research Institutions (implementation standards)" (decided by the Minister of Education, Culture, Sports, Science and Technology on February 15, 2007; revised on February 18, 2014)
- Guidelines for Responding to Misconduct in Research Activities (the Ministry of Economy, Trade and Industry (METI) on December 26, 2007; finally revised on January 15, 2015)
- Guidelines for Responding to the Misuse of Public Research Funds (the Ministry of Economy, Trade and Industry (METI) on December 3, 2008; finally revised on January 15, 2015)

(3) Submission of R&D Plans and Reports

With regard to awarded projects, please note that the R&D Plan and some reports may be required to be submitted in English.

(4) Elimination of Unreasonable Duplication or Excessive Concentration of Research Funds

(a) Measures to prevent unreasonable duplication

In the case that a researcher is unnecessarily being allocated competitive research funds from the national government and/or multiple independent administrative corporations for the same research project (name or content of the research receiving R&D funds) being conducted by the same researchers and any of the following applies, the R&D project may be eliminated from eligibility for review, the decision to adopt the R&D project may be cancelled, or the amount of funds reduced (hereinafter referred to as "Cancellation of decision to adopt, etc.").

- Applications are submitted simultaneously for R&D projects that are essentially the same (including if the projects overlap to a considerable degree; the same shall apply hereinafter) and multiple R&D projects are adopted
- Applications are repeatedly submitted for R&D projects that are essentially the same as an R&D project that has already been adopted and been allocated competitive research funds
- The is duplication regarding the use of research funds amongst multiple R&D projects
- Other equivalent cases

Although there are no restrictions on submitting applications for other competitive research funds at the stage of applying for this program, please notify AMED staff in charge of this program promptly in the case that your R&D project is adopted by another competitive research funding program. If this is not reported, there is the possibility that the decision to adopt the R&D project under this program will be cancelled.

(b) Measures to prevent excessive concentration

Even if the content of the R&D proposal submitted for this program differs from the content of R&D being implemented under another competitive research funding program, in the case that the overall research funds allocated to the relevant researcher or research group (hereinafter referred in this item as "Researchers, etc.") in the relevant fiscal year exceeds the limit that can be used effectively and efficiently and cannot be used completely within the research period, and any of the following apply, the decision to adopt the R&D project under this program may be cancelled.

- Excessive research funds are allocated in comparison to the researcher's abilities or research methods
- Excessive research funds are allocated in comparison to the effort allocated to the relevant R&D project (percentage of the researcher's overall work time* that is needed for implementing the relevant research)
- Unnecessarily expensive research equipment is purchased
- Other equivalent cases

*Based on the Council for Science, Technology and Innovation's definition of "effort": the percentage of researcher's time exclusively spent for the R&D activities concerned against the researcher's annual working hours. Research's total working hours refer to not only the time spent in research activities but also total substantive working hours, including educational/medical activities and administrative duties.

Accordingly, in the case that an application for an R&D project is submitted to and adopted by another competitive research funding program after an application documents for the R&D project has been submitted to this program, or if changes are made to the information provided on the application documents, please report this promptly to the AMED staff in charge of this program. If this is not reported, there is the possibility that the decision to adopt the R&D project under this program will be cancelled.

(c) Provision of information related to application content in order to eliminate unreasonable duplication/excessive concentration

In order to eliminate unreasonable duplication/excessive concentration, information related to parts of the application content (or awarded project/program content) may be provided within the necessary extent, to the persons in charge of other competitive research funding programs, including other government ministry/agency programs, via the Cross-ministerial Research and Development Management System (e-Rad). Furthermore, in

the case that information is requested for checks being conducted under other competitive research funding programs, information may be provided in this way.

(d) Status of application acceptance under other competitive research funding programs, including other government ministry/agency programs

Applicants may be required to provide information in proposal documents regarding the status of application acceptance under other competitive research funding programs, including other government ministry/agency programs (name of program, name of R&D project, project implementation period, budget amount, effort, etc.) In the case that the information provided is factually inaccurate, the R&D project application may be rejected, the decision to adopt the R&D project may be cancelled, or the amount of funds allocated to the R&D project may be reduced.

Ⅵ. Management and Evaluation of Awarded Projects

1. Project Management

- After a proposal is selected, the R&D PI will prepare an overall R&D plan covering the entire R&D project period (up to five-and-a-half years for AMED-CREST and up to three-and-a-half years for PRIME.) The R&D PI will also prepare annual R&D plans for each year of the project. R&D plans include information on the R&D budget and R&D system. Proposed R&D plans (both overall and annual) are decided following verification and approval by the PS and PO.
- Proposed R&D budgets undergo assessment during the selection process. Actual R&D budgets are decided following verification and approval by the PS and PO when the R&D plans are prepared.
- The PS and PO will offer advice and coordinate assistance with regard to the R&D plan and provide instructions when necessary, based on, for example, the project selection process, discussions with R&D PI and the results of R&D evaluations. In order to achieve the overall objectives of the program, the PS and PO may merge or link R&D projects, or take other such coordinative actions.

  *R&D organizations and budgets prescribed in R&D plans may be revised during the R&D project period in response to the overall program budget conditions, R&D Area management actions taken by the PS and PO or factors such as the results of R&D evaluations.

A Contracted R&D Accomplishments Report is required to be submitted each fiscal year for all awarded projects. Furthermore, the PS and PO shall carefully manage progress of the project.

In implementing progress management, exit strategies shall be realized through the implementation of project progress meetings, questionnaires (documents to be completed with details on R&D progress status), hearings (interviews for individual projects), and site visits (confirming the actual status of R&D at the facility carrying out the research), so please cooperate in these activities. Please note that, depending on the progress status, review of the project plan or cancelation (early conclusion) of the project may be required.

For research undertaking investigator-initiated trials or clinical trials with a view to creating innovative drugs or medical devices, or nonclinical studies aimed at conducting such trials* during the R&D period, research institutes are required to submit materials related to the clinical research such as a protocol (including information such as aims, subjects, selection criteria, exclusion criteria, number of cases, observation content, intervention content, statistical methods, and research system).

*Note: Does not include clinical research that is not aimed at creating new drugs or medical devices or that differs from normal processes for evaluating/approving new medical technology.

2. Evaluation

Under this program, awarded projects whose planned project period is five years or longer shall undergo an interim evaluation by the "Project Evaluation Panel" at round the third year after the R&D commences to rigorously evaluate the degree to which the R&D plan is being achieved and R&D accomplishments, etc.* Awarded projects whose planned project period is less than five years are not required to undergo an interim evaluation as a general rule, but in the case that it becomes necessary to conduct an interim investigation in the course of implementing the program, an interim evaluation shall be conducted by the "Project Evaluation Panel".

Furthermore, in the case that it is deemed necessary, R&D projects under this program shall undergo an interim evaluation, regardless of the timing. Based on evaluation results, AMED may decide to cancel (prematurely conclude) or extend a project in accordance with the overall decision of the PS and PO, etc.

Note1: In PRIME, no interim evaluation is performed, except in specific cases and when deemed necessary.
Note2: The results of interim evaluations etc. should be reflected in subsequent R&D revisions and resource allocations (including increases or decreases in R&D budgets, changes in R&D unit structure, etc.) On occasion, measures such as actions to terminate an R&D project may be taken.

In addition, all awarded projects are to undergo ex-post evaluations at an appropriate time following the conclusion of the R&D project. Based on the evaluation results, it may be decided to extend for one year the R&D period of projects that can be expected to lead to practical application and that should be continued developmentally. Moreover, a follow-up evaluation may be carried out after a certain period of time after conclusion of the project if deemed necessary.

3. Presentations at Accomplishments Report Meeting

As part of achievements reporting under this program, the PI of an awarded project shall be required to make a public or closed-door presentation at an Accomplishments Report Meeting held by AMED. In addition, as part of follow-up examinations and examinations of further development of project accomplishments, the PI of an awarded project may be requested, if necessary, to make a presentation in or after the fiscal year in which the project was completed, so please cooperate with this request.

Ⅶ. Handling of R&D Accomplishments

With regard to the handling of R&D accomplishments, research institutes (contractors) are obligated under contracted R&D agreements to strictly comply with items regarding IP rights and usage of research accomplishments.

1. Submission and Publication of Contracted R&D Accomplishments Reports

Contractors shall submit a contracted R&D accomplishments report summarizing the research accomplishments of the R&D project. Please note that the deadline for submission of reports is within 61 days from the end of the term of the contracted R&D agreement or from the conclusion/cancellation/discontinuance of the contracted R&D, whichever comes first. In the case that the contracted R&D accomplishments report is not submitted by the deadline, it shall be deemed that the contracted R&D agreement has not been fulfilled and payment of contracted R&D funds cannot be made, so please be sure to strictly comply with the submission deadline.

In addition, the content of some items in the contracted R&D accomplishments report and the content of general research reports comprise information for public disclosure and shall be published on the AMED website at an appropriate time.

2. Attribution of R&D Accomplishments

Patent rights, copyright, and other IP rights obtained through implementation of the R&D project can revert to the contractor under certain conditions in accordance with the Japanese version of the Bayh-Dole Act under the Industrial Technology Enhancement Act (Law No. 44 of 2000). The purpose of the Japanese version of the Bayh-Dole Act is to invigorate R&D activities through the reversion of IP rights to contractors so that the results of these R&D activities can be used in business activities. Under this program, it is expected that contractors themselves will make the maximum effort to achieve practical application of their research accomplishments, and for this reason the Japanese version of the Bayh–Dole Act has been applied. For details regarding conditions, please refer to contracted items prescribed under the contracted R&D agreement at the time the agreement is concluded.

In owning IP rights related to the results of R&D contracted by the Japanese Government, contractors are in a position whereby they should make maximum efforts to achieve practical application of their R&D accomplishments themselves and be deeply conscious of the expectations being held for the realization of research accomplishments' practical application. In particular, in accordance with AMED's IP policy,* contractors should ensure that appropriate measures have been implemented amongst the contractor's funding sources, such as appropriating indirect costs, in obtaining IP rights in order to ensure appropriate protection and utilization of IP rights on a global scale.

AMED's Department of Intellectual Property provides consistent support for maximizing and achieving practical application of R&D accomplishments that have reverted to contractors.

Support provided by AMED's Department of Intellectual Property includes (1) support for strengthening intellectual propertization of research accomplishments, (2) advice for business collaboration strategies, and (3) support for activities leading to businesses or licensing.

*http://www.amed.go.jp/chitekizaisan/chizai_policy.html

3. IP Educational Materials for Medical Researchers

IP educational materials for medical researchers is provided on the AMED website* as a reference for considering strategies for submitting applications for, obtaining patent/IP rights for, and utilizing R&D accomplishments that have reverted to contractors. Researchers are strongly recommended to peruse these IP educational materials prior to carrying out research.

*http://www.amed.go.jp/chitekizaisan/chizai_kyouzai.html

4. Securing Open Access to R&D Accomplishments

Having secured the necessary IP rights, contractors are requested to cooperate in ensuring open access to research accomplishments as far as possible.

Ⅷ. Handling of Acquired Goods

1. Ownership

Ownership of goods, etc. acquired by Universities and Research Institutions,[1] through direct costs (hereinafter referred to as "Acquired Goods") shall revert to the university, etc.

Ownership of acquired goods by Companies, etc.,[2] shall revert to AMED in the case of goods with an acquisition cost of 500,000 yen or more (consumption tax included) and has a service life of one year or more, but the relevant acquired goods may be used free-of-charge for the purpose of contracted R&D by the contractor until the conclusion of the contracted R&D period. The contractor shall manage the relevant acquired goods properly with the due diligence of a prudent manager.

[1]"Universities and research institutions" include:
(i) Incorporated educational institutions such as national university corporations, public universities, and private universities
(ii) Public research institutions such as national research institutes, public research institutes, and independent administrative corporations
(iii) Organizations with a public nature, such as public-service corporations, that are recognized by AMED.

[2]"Companies, etc." is a general term for research institutes other that "universities, etc."

2. Handling of Acquired Goods after Completion of R&D Period

For the purpose of continued application of the relevant R&D, as a general rule an enterprise, etc., may continue to use free-of-charge tangible property acquired in or after FY2015 and whose ownership has reverted to AMED for the duration of its service life and the tangible property may be transferred to the enterprise, etc., for a fee after its service life has passed, provided that this shall not apply in either case in the event that AMED uses or disposes of the relevant acquired goods.*

With regard to acquired goods that are treated as consumables, no specific leasing agreement or other procedures will be implemented, but the contractor shall manage the relevant acquired goods properly with the due diligence of a prudent manager until their use is finished (resale of acquired goods for profit is not permitted).

*The above are the general rules for handling of acquired goods, but changes may be made. Formation regarding handling of acquired goods will be provided again at the time of leasing agreement, sales agreement, and/or transfer procedures following the conclusion of the R&D project.

3. Disposal of Radioactive Waste

It is the responsibility of the contractor to dispose of contaminated property and/or radioactive waste generated through implementation of the R&D project.

Ⅸ. Other

1. Two-way Communication with the General Public

In accordance with the “Promotion of the 'Dialogue on Science and Technology with Citizens' (A Basic Course of Action)” (decided by the Minister of State for Science and Technology Policy and the Executive Members of the Council for Science and Technology Policy on June 19, 2010), the Council for Science and Technology Policy (now the Council for Science, Technology and Innovation) requires not only that science and technology results are returned to the general public, but also that the content and results of R&D activities be explained to society and the general public in an easy-to-understand manner from the standpoint that it is imperative to take the stance of obtaining the general public’s understanding and support as well as promoting science and technology in order to generate outstanding science and technology results without pause, further advancing Japan’s science and technology. Accordingly, research institutes are requested to proactively undertake measures to continuously disseminate information about research activities, such as holding public lectures or symposiums on research accomplishments and/or continually posting research accomplishments on the Internet.

Reference: Regarding the Promotion of Dialog with Citizens on Science and Technology (basic initiative guidelines)
http://www8.cao.go.jp/cstp/output/20100619taiwa.pdf

2. Health Risk Information

In accordance with requests from the Ministry of Health, Labour and Welfare, AMED requires researchers to report information obtained in the process of conducting research that could seriously threaten the lives and/health of members of the general public (hereinafter referred to as “Health risk Information” to the Ministry of Health, Labour and Welfare using the prescribed form. For details such as contact information, please refer to the AMED Administration Manual for Contracted R&D Agreement in Japan Agency for Medical Research and Development.[2]

The health risk information provided is evaluated together with other information by the Ministry of Health, Labour and Welfare and used in considering necessary responses to the relevant health risk. Providing this information does not place responsibility on the researcher, so please provide a broad range of information.

[1]http://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/kenkoukiken.doc
[2]Link from http://www.amed.go.jp/program/youshiki.html

3. Information for inputting data into the Government Research and Development Database

Research carried out using contracted R&D funds is targeted for input into the Government Research and Development Database (Council for Science, Technology and Innovation, Cabinet Office), which is a cross-ministerial R&D database. Please submit the following information to the Government Research and Development Database via e-Rad.

(1) Researcher ID number (8 digits)

The unique number issued by e-Rad to individual researchers is called the “Researcher ID number”. Under the e-Rad system, individual researchers are issued with a “Researcher Number” for handling basic information for the relevant R&D program/project such as the name of the research project, names of researchers, research implementation period, and budget amount in order to ensure the uniqueness of each researcher.

Note: The “Researcher Number” differs from “Researcher ID”.

(2) Effort

The PI should provide figures for the number of hours a researcher requires to carry out the relevant research that comprise the total number of working hours of that researcher (including hours worked outside regular working hours) (so-called “Effort”) expressed as a percentage (rounded off the two decimal places).

Because researchers on the relevant project do not bear a certain percentage of total “effort”, please make sure there are no mistakes in your calculations.

$$\text{Effort rate for Researcher A (\%)} = \frac{\text{Hours required for Researcher A to perform the relevant research}}{\text{Researcher A's total annual working hours}} \times 100$$

(3) Research fields on the "Research Field Particulars and Key Words List"

With regard to research fields that are related to the principal field of research ("Research Field (Principal)" ("Research Field (Secondary)"), selected the research field from the "Research Field Particulars and Key Words List" and input the research field, research category, research field, particulars number, and particulars name. In addition, with regard to key words for the content of the relevant research, please select key words from the "Research Field Particulars and Key Words List" and input the key word number and key word (minimum of one, maximum of five).

When inputting key words, you must select a minimum of one key word from the "Research Field Particulars and Key Words List"; however, when you wish to input key words that are no on the "Research Field Particulars and Key Words List", please input a maximum of two key works in 50 letters/characters or less in the "Other Key Words" column. Accordingly, it is possible to input a maximum of seven key words.

(4) Nature of the R&D

Please indicate whether the relevant R&D is basic research, applied research, or developmental research.

4. Smoothing Utilization of Research Tool Patents

With regard to research tool patents, please endeavor to handle research tool patents appropriately in accordance with the Guidelines for Facilitating the Use of Research Tool Patents in the Field of Life Sciences (Council for Science and Technology Policy (now the Council for Science, Technology and Innovation), March 1, 2007.

5. Measures Related to the IP Strategic Program

The "IP Strategic Program" is a program formulated every year by Intellectual Property Strategy Headquarters in accordance with the Intellectual Property Basic Act (Act No. 122 of 2002) with the aim of promoting strengthening of IP strategies. Under the Intellectual Property Strategic Program 2014 (Intellectual Property Strategy Headquarters on July 4, 2014),[1] strategic utilization of certification is to be promoted in order to further invigorate international standardization activities, and AMED is also to promote R&D with a view to international standardization/certification.

Accordingly, in the case that a public research institute is using contracted R&D funds to carry out R&D with the potential to lead to international standardization/certification, the research institute is requested to undertake R&D with a view to international standardization, such as considering support when instigating certification activities for incorporating formulation of standards for certification into individual R&D plans and including the participation of certification organizations in R&D activities.

[1]Intellectual Property Strategic Program 2014 (excerpt)
http://www.kantei.go.jp/jp/singi/titeki2/kettei/chizaikeikaku20140704.pdf
First pillar: Building up a global IP system for enhancing industrial competitiveness
4. Efforts for international standardization and certification
(2) Measures to be taken in the future
(Promoting international standardization strategies in specific strategic fields[2])

・With regard to international standardization strategies in specific strategic fields (with the fields selected based on market scale and growth potential, expandability of the field, Japan's superiority in the field, and the significance of international standardization), the Government of Japan will take the lead in international discussions and facilitate voluntary efforts made by interested parties (short term and medium term) (Cabinet Secretariat, Cabinet Office, MIC, MEXT, Ministry of Health, Labor and Welfare [MHLW], MAFF, METI, Ministry of Land, Infrastructure, Transport and Tourism [MLIT], Ministry of the Environment [MOE]).

[2]"Specific strategic fields": (1) Advanced medical technology, (2) Water, (3) Next generation vehicles, (4) Railways, (5) Energy management, (6) Digital content, (7) Robots

6. Support for Formulation of IP Strategies by AMED IP Consultants

AMED shall provide consistent support in order to promote the practical application of research accomplishments obtained through programs implemented by AMED. Specifically, AMED provides (1) support for strengthening related to intellectual propertization of R&D results such as consultation for improving written descriptions and advice for addition data; (2) advice regarding business collaboration strategies connected to IP for moving R&D to the developmental stage; and (3) support for detailed investigation and proposal formulation of IP strategies/exit strategies under R&D plans through collaboration with AMED IP consultants and the relevant AMED departments/offices, beginning with support for activities leading to businesses or licensing. AMED therefore

provides information necessary for achieving practical application of research accomplishments (information on IP and R&D plans) (please refer to Chapter IV. 1.). In addition, AMED plans to implement hearings as necessary.

If you wish to receive support for formulating proposals for IP strategies/exit strategies, please contact AMED's Medical IP Desk. Please refer to the website below for information regarding the Medical IP Desk.

7. Support from the AMED Drug Discovery Support Network/Department of Innovative Drug Discovery and Development

In order to link the results of outstanding basic research by universities to the practical application of drugs, AMED's Department of Innovative Drug Discovery and Development (hereinafter referred to as the "Drug Development Department" functions as headquarters for constructing a nationwide "Drug Discovery Support Network" comprising the Institute of Physical and Chemical Research (RIKEN), National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN), National Institute of Advanced Industrial Science and Technology (AIST), and other institutions. Network activities include providing continuous support for practical application related to drug discovery research, mainly from the applied study stage through to the preclinical development stage, as well as business derivation.

The Drug Development Department provides a wide range of consultation services for researchers undertaking drug discovery research as part of programs implemented by the Department, as well as gathers, examines, and evaluates information regarding promising R&D seeds; formulates R&D plans (including exit strategies) aimed at IP strategies for individual R&D seeds and collaboration with drug companies; provides technological support for applied research (exploratory study, optimization study, etc.) and nonclinical studies (conforming to GLP (Good Laboratory Practice)); introduction and contracted support of CROs (Contract Research Organizations) and CMOs (Contract Manufacturing Organizations), etc.; and procedures for collaboration with drug companies.

In this way, the Drug Development Department is a department that specializes in providing advice on technological projects related to practical application to researchers at universities, etc., engaged in drug discovery research, as well as support for formulating R&D strategies aimed at collaboration with drug companies. For this reason, R&D projects commissioned by AMED that are related to drug development may receive active support from the Drug Development Department in coordination with the relevant departments/offices.

Accordingly, information regarding applications for R&D projects related to drug development shall be provided to the Drug Development Department, regardless of whether or not the project is adopted under this program (please refer to Chapter IV. 1.). Furthermore, the Drug Development Department provides the above-mentioned support based on requests by researchers on the premise of maintaining confidentiality and protecting IP rights that have reverted to the researcher.

Please refer to Chapter X. for references related to support provided by the AMED Drug Discovery Support Network and the Drug Development Department.

8. Enhancement of AMED Project Evaluations

With the aim of enhancing the Project Evaluation Panel and conducting even more appropriate evaluations, AMED is endeavoring to secure panel members with a high degree of knowledge in specialized fields and pace careful attention to membership diversity from the perspectives of age, gender, and affiliated institution. For this reason, in the case that a R&D project is adopted under this program, AMED may request that researchers provide their cooperation as AMED Project Evaluation Panel members.

9. Government expense categorization table

This program sets out the cost structure as shown below according to the government expense categorization table commonly used for competitive funds. Refer to the table on the website below.

http://www.mext.go.jp/a_menu/shinkou/hojyo/1311601.htm (only Japanese)

10. Diversion of costs between categories

Certain amount of an item of Direct Costs may be appropriated to another item of Direct Costs if such treatment is necessary for the performance of the Contracted Research and Development; provided, however, that the prior approval of AMED shall be obtained if the amount per item of such treatment exceeds fifty percent (50%) of Direct Costs (or five million yen (JPY 5,000,000), if an amount equal to fifty percent (50%) of Direct Costs is less than five million yen (JPY 5,000,000)).

11. Regarding the securing of research time by the end of the fiscal year

The following responses will be made in order to ensure that the research can be conducted by the end of the fiscal year, pursuant to the contracted R&D agreement. Research instituion shall make report the contents of Outcome and submit Report of Outcome to AMED, in accordance with Administrative Manual and instructions of AMED, by the last day of May after expiration the Current Fiscal Year or by the date within sixty-one (61) days after expiration of project designated by AMED. Research institution shall submit an interim report on Outcome as necessary. Research institutions are requested to make efforts to prepare the requisite systems within their organizations with the full understanding that the deadlines are set as above in order to secure sufficient time for the research before the end of the fiscal year.

12. Regarding the encouragement of shared use of research facilities and equipment

According to the "Competitive Research Fund Reform toward Sustainable Creation of Research Results) (interim report)" (Investigative Commission on Competitive Research Expenditures Reform on June 24, 2015), with the adequate fulfillment of targets as a prerequisite, it would in principle be appropriate for highly versatile and comparatively large facilities and equipment to be shared.

In addition, the document entitled "Introduction of New Research Facility/Equipment Sharing Integrated with Research System Management" (Sub-committee, Council for Science and Technology of Advanced Research Infrastructure in November 2015) requests that a sharing system for the use of facilities and equipment at research organization level is established at universities and national research institutions (hereinafter "the equipment sharing system").

In response to this, with regard to research facilities and equipment purchased for the program, particularly large and versatile items, participants are requested to enthusiastically buy and share facilities and equipment purchased for other research and by combining research funds for multiple projects, within the scope of the management conditions of other research funds and pursuant to the equipment sharing systems of the institutions or organizations they are affiliated to, and to an extent that will not obstruct the promotion of the AMED-CREST and PRIME research projects.

Furthermore, participants are also asked to collaborate eagerly in "University Collaboration Network for Efficient Utilization of Research Equipment" that is being established nationally for mutual use by the National Institutes of Natural Sciences' Institute for Molecular Science and "Equipment Support Center Development Project" run by the national universities, both of which are creating cross-university sharing systems, and to actively promote shared use of research facilities and equipment in an inter-research organizational and institutional manner.

*Introduction of New Research Facility/Equipment Sharing Integrated with Research System Management (Sub-committee, Council for Science and Technology of Advanced Research Infrastructure on November 25)
http://www.mext.go.jp/component/b_menu/shingi/toushin/__icsFiles/afieldfile/2016/01/21/1366216_01_1.pdf (in Japanese)

*Competitive Research Fund Reform toward Sustainable Creation of Research Results) (interim report) (Investigative Commission on Competitive Research Expenditures Reform on June 24, 2015)
http://www.mext.go.jp/b_menu/shingi/chousa/shinkou/039/gaiyou/1359306.htm (in Japanese)

*Unification of the use rule, etc. in the competitive fund (The agreement at the liaison meeting of relevant Ministries on the competitive fund on March 31, 2015)
http://www8.cao.go.jp/cstp/compefund/siyouruuru.pdf (in Japanese)

*University Collaboration Network for Efficient Utilization of Research Equipment
https://chem-eqnet.ims.ac.jp/ (in Japanese)

13. Regarding the improvement of incentives for students in the latter term of doctoral course

The third, fourth and fifth Science and Technology Basic Plan of the Japanese government, in an attempt to lure outstanding students and experienced professionals form within and outside Japan, states as one of their numerical targets to implement financial aid for doctorate students attending the latter part of the course: "We will strive to enable 20 percent of doctoral students to receive an amount equivalent to their living expenses."

Furthermore, "Graduate School Education Reform for the Future (Summary of Discussions)" (Working Group on Universities, Central Council for Education on September 15, 2015) calls for improvements to employment of doctorate students in the latter half of their courses as research assistants (RA) with varied funding, and the paying of wages and salaries to cover their living expenses as a fundamental in the hiring of RAs and TAs who are doctorate students in the latter stages of their courses.

In response to the above considerations, this program will positively recruit doctorate students in the latter term of their course as RAs, aim to pay them a wage commensurate with their living expenses, and try to set wage levels at a level that reflects the amount of time they work.

14. Regarding support for diverse career paths for young postdoctoral researchers

According to the "Basic Policy on Support for Diverse Career Paths for Young Postdoctoral Fellows to Be Employed through the MEXT Public Research Funds" (formulated on December 20, 2011 by MEXT's Science and Technology Academic Council's Personnel Committee, and details of which can be viewed (in Japanese) here: http://www.mext.go.jp/b_menu/shingi/gijyutu/gijyutu10/toushin/1317945.htm), "The public research institutions and their representatives should eagerly involve themselves in the support of young postdoctoral researchers in order to secure for these young people a variety of career paths inside and outside of Japan." In response to this statement, those involved in the projects adopted as a result of this current solicitation for proposals are requested to pursue positive initiatives to secure a variety of potential career paths for young postdoctoral researchers employed using the competitive funds, funding from other research projects, solicitation-based education and research funds aimed at universities, or other public research funds.

In addition, please consider the use of indirect costs for the funding of these initiatives.

15. Provision of Information from e-Rad to the Cabinet Office

According to the 5th Science and Technology Basic Plan (approved by Cabinet decision in January 2017), the government evaluates and analyzes competitive research funding systems in Japan using the information in e-Rad to pursue effective science and technology policy. CSTI and relevant ministries to link the investments by competitive research funding systems with outcome of them for the purpose of evaluating of competitive research funding systems and making plans for effective and efficient total strategies and a policy of resources allocation

Furthermore, researchers and research institutions will be required to register information of R&D accomplishments such as published papers and patents and accounting reports every fiscal year. In addition, the information in e-Rad including accomplishments and accounting reports will be provided to the Cabinet Office for macroanalysis.

16. Regarding registration with researchmap

As the largest directory of researchers in Japan, researchmap (formerly called "ReaD&Researchmap", http://researchmap.jp/) is a researcher informaton database. The information registard by the researcher on his/her own research track record can optionally be made accessible to the Internet. In addition, the compatibility of research with other systems, which enables access to its registered information, allows it to link with other databese systems, thereby saving researchers from repetitiously entering the same research record information on multiple applications and databeses.

The information registerd at researchmap is put to use in national and other academic and science and technology policy formulation research, as well as being used for statistical objectives, so those implementing the program are requested to be sure to register with researchmap.

17. Cooperation with Databases

(1) National Bioscience Database Center

- The Japan Science and Technology Agency National Bioscience Database Center (NBDC)* provides the Life Science Database Archive (http://dbarchive.biosciencedbc.jp/) from which complete sets of data generated by researchers in the life science field in Japan can be downloaded. The Center also provides data related to human bioscience through the NBDC Human Database (http://humandbs.biosciencedbc.jp/), a platform for sharing various data generated from the human genome and other human-derived specimens.
- To enable research accomplishments data in the bioscience field to used widely and for a long time, please cooperate in contributing data to the NBDC "Life Science Database Archive" and/or "NBDC Human Database".
- Contact: The Japan Science and Technology Agency National Bioscience Database Center (NBDC)
  Inquiries regarding the Archive: dbarchive"AT"biosciencedbc.jp
  Inquiries regarding the Human Database: humandbs"AT"biosciencedbc.jp
  (Change "at" to @ when inputting the address.)

* National Bioscience Database Center (http://biosciencedbc.jp/) provides R&D and services for making it easier to integrate and use Japanese bioscience-related databases with the aim of invigorating research and development through widespread sharing and utilization of research data.

(2) Deposit of Developed Resources to the National Bioresource Project (NBRP)[1]

So that the persons implementing this program contribute to research in the life science field, after using bioresources developed under this program and publishing the research accomplishments obtained via academic papers, etc., as a general rule researchers are to deposit the relevant bioresources to institutions participating in the NBRP Core Facility Upgrading Program[2] (limited to bioresources targeted by the NBRP), making these resources broadly available for researchers' use.

[1]National Bio Resource Project (NBRP): http://www.amed.go.jp/program/list/04/01/043.html

[2]"Contribute": Procedure for permitting the use of resources in resource programs (storage/provision) without transferring various rights related to the relevant resources. By prescribing conditions for provision within the contribution consent form, it is possible to add conditions regarding restrictions on use of resources and use of extracts from academic papers, etc., for users receiving the relevant resources.

(3) Other

With regard to specimen storage and genome analysis, R&D projects are required to actively use existing research bases, and AMED may in some cases provide guidance regarding/matching with the most suitable research bases. Accordingly, please cooperate in the event that AMED requests that the R&D project provides data to various databases designated by AMED, including in response to the above.

X. References

If you should have any questions regarding the content of these application guidelines, please make inquiries via the contact addresses provided in the table below.[1, 2] In addition, in the case that any information provided here changes, these changes shall be posted in the AMED website under "Collaborative Calls Information" [3], so please check the website for updates.

[1]Please make inquiries by e-mail as far as possible (Change "at" to @ when inputting the address.)

[2]Be careful to dial the correct telephone number. Unless otherwise stated, telephone inquiry services are available 10:00–12:00 and 13:00–17:00 weekdays.

[3] http://www.amed.go.jp/koubo/010720170310-01.html

Content of inquiry	Contact address
R&D projects being solicited; how to fill in review/proposal documents	AMED Department of Research Infrastructure, Division of Emergening Research Tel: +81-3-6870-2224 E-mail: kenkyuk-kobo"AT"amed.go.jp
Misconduct/fraudulent use/fraudulent receipt	AMED Department of Research Integrity and Legal Affairs E-mail: kouseisoudan"AT"amed.go.jp
Management of conflict of interest/research ethics education programs	AMED Department of Research Integrity and Legal Affairs E-mail: kenkyuukousei"AT"amed.go.jp
Support provided by the AMED Drug Discovery Support Network/Department of Innovative Drug Discovery and Development	AMED Department of Innovative Drug Discovery and Development West Japan Office Tower B, Grand Front Osaka, 1 3-chome Ofuka-cho, Kita-ku, Osaka City, Osaka Prefecture, Japan. 530-0011 Tel: +81-6-6372-1771 (Extension 120) E-mail: id3navi"AT"amed.go.jp
How to use the e-Rad system	e-Rad Portal Site Help Desk Before telephoning, please check the "Frequently Asked Questions (FAQ)" page. Link from: https://www.e-rad.go.jp/contact/ →After checking the FAQ page, log in to e-Rad so that you can check the operation manual, then dial: Tel: 0570-066-877 (NAVI-DIAL) or +81-3-5625-3961 (direct line) if the NAVI-DIAL service is unavailable. Operating hours: 9:00–18:00 (weekdays) *Excludes Saturdays, Sundays, public holidays, or Year-end/New Year holidays (December 29 – January 3)
Bioscience Database Life Science Database Archive	Japan Science and Technology Agency (JST) National Bioscience Database Center (NBDC) E-mail: dbarchive"AT"biosciencedbc.jp http://dbarchive.biosciencedbc.jp/
Bioscience Database NBDC Human Database	Japan Science and Technology Agency (JST) National Bioscience Database Center (NBDC) E-mail: humandbs"AT"biosciencedbc.jp http://humandbs.biosciencedbc.jp/
AMED's IP policy and handling of IP in contracted R&D projects	AMED Department of Intellectual Property Tel: 03-6870-2237 Email: medicalip"AT"amed.go.jp

XI. R&D Area Being Solicited

The R&D Area for which applications are being solicited is as follows. For an overview of this entire program, please refer to Chapter I; for application/selection implementation methods, please refer to Chapter III.

R&D Area for the Research and Development Objective: "Clarification of the mechanism of individual functional impairment over the entire life course"

1. Clarification of the mechanisms of individual functional impairment over the entire life course

Program Supervisor (PS): Eisuke Nishida, Professor, Graduate School of Biostudies, Kyoto University
Program Officer (PO): Eiji Hara, Professor, Research Institute for Microbial Diseases (RIMD), Osaka University

Outline of the Research and Development Program

In this R&D area, we aim to clarify the individual functional impairment mechanism over the entire life course, enabling evaluation and control of functional impairment, and creating the seeds for future health and medicine.

From birth to death, organisms are constantly subject to various stimuli from the environment. These physical stimuli such as temperature, humidity, oxygen, and light, and factors external to the individual such as nutritional and sanitary status have an effect on internal and genetic factors. It is becoming apparent that by having an impact over the long term, it ultimately causes individual functional impairment. It has also been suggested that the reaction to stimuli from the external environment could affect the functions of the next generation.

If it were possible to prevent this individual functional impairment, it would be possible to provide new means for maintaining and improving quality of life, which depends on the treatment of individual diseases. Consequently, it is important to identify the factors causing individual functional impairment, understand the mechanisms involved, and become able to evaluate and control the functional impairment. Providing a scientific basis for health promotion methods and methods of disease prevention and intervention through lifestyle, exercise and diet, and creating the seeds of new technologies and industries such as discovering drug development targets for diseases and developing food products with health-promoting functions offer promise.

However, basic mechanism, that is, what factors in the individual are responsible for remembering the reaction to stimuli and so on from the external environment and how that memory impacts individual functions over a long period and causes individual functional impairment as a result, is largely unknown. For understanding and being able to control the very complex phenomenon of individual functional impairment, it is important to adopt a research system with cooperation between researchers in a wide range of research fields such as birth, immunity, stem cells, protein quality control mechanisms, and epigenetics.

In this R&D area, we seek to clarify the mechanism of functional impairment over the entire life course by gathering researchers from fields related to individual functional impairment and promoting mutual cooperation. In addition, we will work to create the seeds of basic technology for evaluation and control of individual functional impairment.

Policy of the Program Supervisor and Program Officer on call for application, selection, and project management

In this R&D area, we aim to identify the causes leading to individual functional impairment over the entire life course, and clarify the mechanisms involved. In addition, we will promote the creation of the seeds of basic technology for evaluation and control of individual functional impairment.

Therefore, besides research fields such as birth, immunity, stem cells, protein quality control mechanisms, and epigenetics, we will seek cooperation in a wide range of research fields including nutrition, hygienic environment, sleep, and circadian rhythm. Undertaking research with new perspectives to elucidate the mechanism of individual functional impairment is expected to lead to the creation of the seeds of basic technologies for evaluating and controlling functional impairment.

In this R&D area, we will solicit research proposals focusing on functional impairment over the biological life course and in the individual overall, such as analysis of the factors causing individual functional impairment over the life course and the mechanism involved, how functional impairment of certain organs affects functional impairment of the individual as a whole, and how environmental conditions such as nutrition and the hygienic environment affect functional impairment. We will also solicit research proposals focusing on creating technologies for evaluating and controlling functional impairment.

(1) AMED-CREST (unit-type)

In this R&D area, we will solicit proposals for innovative basic research using interdisciplinary approaches to identify the causes leading to individual functional impairment over the entire life course and to clarify the mechanisms involved. We will also solicit research proposals for creating indices for evaluating individual functional impairment and the seeds of basic technologies aimed at controlling it.

For understanding and being able to control the very complex phenomenon of individual functional impairment, we believe it is desirable to organize a research unit comprising several research fields. We also welcome proposals from researchers who are actively undertaking cooperation across different fields in promoting the research.

The following areas are shown as examples of anticipated R&D proposals, but we also hope for original research proposals too.

- Clarification of the mechanisms by which environmental conditions such as nutrition and hygiene affect individual functional impairment
- Clarification of the mechanism of systemic functional impairment, focusing on functional impairment of stem cells
- Analysis of the effect of homeostatic mechanisms such as protein quality control on individual functional impairment
- Analysis of the effect of specific organ functional impairment on the individual as a whole
- Analysis of the effect of circadian rhythm and sleep on individual functional impairment
- Analysis and comparison of the functional impairment mechanism across species, such as fruit flies, nematodes, and yeast
- Creation of analytical techniques for individual functional impairment using a systems biology approach

When applying, it is not necessary for participating researchers to be currently undertaking research in individual functional impairment. We welcome innovative proposals from other research fields with scientific rationality.

- We will select approximately 3-6 proposals for AMED-CREST this fiscal year, with a total budget of up to 390 million yen per project for R&D costs (including 90 million yen indirect costs) over the project term. Proposals for more than this limit should not be considered for approval.

(2) PRIME (solo-type)

The PRIME program invites proposals for unique studies that focus on individual researcher's specialty and relate to the same research and development areas as described in the AMED-CREST program. We invite wide-ranging proposals for identifying the causes related to functional impairment over the biological life course or the mechanisms that cause functional impairment, challenging themes that pursue new breakthroughs, and proposals for creating innovative technologies that make significant contributions to basic research (for example, new model organism assays or imaging technology that achieves evaluation of functional impairment).

In the research implementation process, we will not restrict the field of specialties of applicants. We hope that applicants will actively pursue engagement with other research groups within and outside the field, particularly with researchers from the AMED-CREST research units and the AMED Project for "Clarification and Control of the Aging Mechanism", with a view to future application of the findings. Furthermore, as with AMED-CREST, although this is basic research, it is important that it leads to the creation of new health and medical seeds in future. Therefore, the ability to obtain intellectual property rights for the research findings is an important consideration.

- We will select approximately 8-12 proposals for AMED-CREST this fiscal year, with a total budget of up to 52 million yen per project for R&D costs (including 12 million yen indirect costs) over the project term. Proposals for more than this limit should not be considered for approval.

Briefing of Solicitation for this research area is planned as following date. (NOTE: only in Japanese.)
Date: April 28, (Fri.) 14:10 – 14:50
In detail, please refer "III. 2. (5) Schedule for Briefings of Solicitation."

(Reference) Research and Development Objective:" Clarification of the mechanism of individual functional impairment over the entire life course"

1. Title of the Objective

Clarification of the mechanism of individual functional impairment over the entire life course

2. Outline of the Research and Development Program

With the rapid progress of aging in industrialized countries including Japan, extending healthy longevity is an issue of global importance. While treating individual diseases and improving quality of life (QOL) are important for extending healthy longevity, preemptively suppressing functional impairment at the individual level is expected to be an effective approach.

From birth to death, organisms are constantly subject to various stimuli from the environment. It is thought that the long-term effects of these external factors and internal genetic factors cause individual functional impairment. In understanding and controlling this complex phenomenon, there are limits to the conventional research approaches focusing separately on diseases and on tissues and organs. Instead, a strategic approach is necessary.

Therefore, for this R&D objective, we aim to undertake innovative interdisciplinary research across wide-ranging fields such as birth, immunity, stem cells, protein quality control mechanisms, and epigenetics, over the entire life course from birth to maturity, aging, and heredity. We expect this research to identify the mechanisms involved for evaluating and controlling individual functional impairment, and to create the seeds for basic technologies.

3. Goals to be achieved

For this R&D objective, we aim to be able to evaluate and control individual functional impairment, and in addition to conducting research mainly aimed at clarifying the mechanism of individual functional impairment, we will create the seeds for the development of basic technologies. Specifically, we aim to achieve the following;

(1) Identification of the causes leading to individual functional impairment, and clarification of the mechanisms involved
(2) Creation of the seeds of basic technology for evaluation and control of individual functional impairment

4. Research promotion focusing on the future development of our society

By achieving the matters shown in "3. Goals to be achieved, we will contribute to realizing a society with the following characteristics.

- Being able to evaluate and control individual functional impairment rather than focusing on risk factors or disease, will enable the integrated prevention, diagnosis, and treatment of various types of risk and disease. Furthermore, establishing a scientific basis for health promotion methods and methods of disease prevention and intervention through lifestyle, exercise and diet will enable people to lead healthy lives based on correct scientific knowledge. In this way, in addition to extending healthy longevity, we will reduce the burden of care and medical expenses on social security by reducing the population requiring care.
- By clarifying the basic mechanisms behind individual functional impairment, we will discover new drug development targets for aging-related diseases and contribute to the development of food products with health-promoting functions, thereby improving the competitiveness of Japan's pharmaceutical and food product industries.

5. Specific examples of research

(1) Identification of the causes leading to individual functional impairment, and clarification of the mechanisms involved

Conduct interdisciplinary research to identify the causes leading to individual functional impairment over the entire life course and clarify the mechanisms involved. For example, we will analyze the impact of the environmental conditions of birth and the development phase on individual functional impairment, and the impact of homeostatic mechanisms such as the immune system, stem cells, protein quality control mechanisms and epigenetics; analyze homeostatic mechanisms such as cellular aging at the cellular level; analyze

interspecies differences, individual differences, and so on in individual functional impairment using a comparative biological approach.

(2) Creation of the seeds of basic technology for evaluation and control of individual functional impairment

We will create the seeds of basic technologies required for creating indices for evaluating individual functional impairment and technologies for controlling it. For example, we will develop technologies such as imaging technology for chronological visualization of individual functional impairment; quantitative measurement and analysis techniques and data integration technologies using mathematical and engineering approaches; technologies that enable the creation and analysis of multicellular systems that mimic and replicate stress environments, and so on.

6. Research trends in Japan and overseas

Trends in Japan

Japan is in a strong position globally in research fields such as birth, immunity, stem cells, protein quality control mechanisms, and epigenetics which are important for approaching individual functional impairment from a wide perspective. Particularly in recent years, there has been a focus on research into how stimuli from diverse environments are recorded as changes in the intranuclear epigenetics of organisms, with implications along the axis of time, from birth to aging and the next generation. Japanese research groups have announced pioneering findings in these fields. In addition, Japanese researchers have played a major role in identifying the mechanisms of functional impairment in cells and individuals, such as the discovery that cancer-suppressing gene $p16^{INK4a}$ is involved in inducing cellular aging, and the discovery of the Klotho gene that causes a wide range of aging symptoms through mutation.

Trends Overseas

With the rapid advance of aging in industrialized countries, the importance of this research area is increasing globally too. In addition, research to elucidate the individual functional impairment mechanism at the molecular level is making rapid advances, such as the discovery of the functions related to the Sirtuin life cycle and aging control, and the discovery of new roles related to the life cycle and aging control of the signaling pathway of the metabolic system. In the United States the National Institute on Aging (NIA) has been established within the National Institute of Health (NIH), and a budget has been allocated for research not only in these institutions, but also at other institutions in the U.S. In Germany, the Max Planck Institute for Biology of Ageing was established in 2007, and active research is underway in the rest of Europe.

7. History of the investigations

Investigations were conducted as described below, based on the Policy on Defining Strategy Objectives (decision dated 8 June 2015 by the Council for Science and Technology, Strategic Basic Research Programs Subcommittee).

Creation of analysis materials relating to research trends in Japan and overseas through scientometric methods using the Grants-in-Aid for Scientific Research (Kakenhi) database and other sources

Using the Kakenhi database and other sources, we created analysis materials on research trends in Japan and overseas by applying scientometric methods, such as analysis of co-citation and direct citation relations for research papers.

Analysis materials used for a questionnaire-based survey of specialists to identify key research trends

The analysis materials produced were used to run a questionnaire-based survey of key research trends in the future that was submitted to each of the units at the Center for Research and Development Strategy (CRDS), the Program Directors at the Japan Agency for Medical Research and Development (AMED), and the specialists participating in the specialist network of the National Institute of Science and Technology Policy's (NISTEP) Science and Technology Foresight Center. The questionnaire responses were analyzed and "the mechanism of deterioration of organism responsiveness through interaction with the environment" was specified as a key research trend.

Workshops and creation of R&D objective

A workshop was held where experts from the industries relevant to the key research trend of "the mechanism of deterioration of organism responsiveness through interaction with the environment" assembled to discuss key

trends in Japan and overseas, the possible social and economic impact of developments in research and technology development and the possible future of society from these outcomes, and objectives that need to be achieved during the research stages. These workshop discussions were used to develop the R&D objectives.

8. Relevant descriptions included in Japanese Cabinet documents

5th Science and Technology Basic Plan (Cabinet decision dated 22 January 2016)

Chapter 3 (1) <2> i)

Japan has already become the most super-aged society in the world and we need to pursue basic scientific research to develop healthcare technologies and use these results to extend our healthy longevity and ensure the sustainability of our healthcare system.

The Plan for Promotion of Medical Research and Development (approved by the Headquarters for Healthcare Policy, 22 July 2014, partially revised February 17, 2017)

1-1. (1) (a)

In 2013, 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 9.02 years for men and 12.40 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 burden. 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.

The Japan's Plan for Dynamic Engagement of All Citizens (Decided by the Cabinet June 2, 2016)

Living with Confidence (Prevention of frailty of the elderly and countermeasures)

6. Extension of Healthy Life Expectancy to Enable People to Lead Healthy and Abundant Golden Years (Part 2)

Concrete measures

We will promote exercise activities which are easily conducted by encouraging new types of exercises, development and popularization of sports and exercises in familiar places like occupational fields. We will work on enhancement of nursing care prevention programs for the scenes including exercises and sports which can increase motivations of the elderly to be independent. Furthermore, we will promote figure out the aging mechanism.

Japan Revitalization Strategy 2016: Towards the Fourth Industrial Revolution (Decided by the Cabinet June 2, 2016)

Section 2 1-2. (2) <4>

In addition to promoting the creation of industry using local resources such as food and agriculture, tourism and sports, undertake basic research to clarify the diseases peculiar to the elderly and to control aging, and consider implementation of social impact bonds by local government to promote the development of industries directed towards extending healthy longevity.

9. Miscellaneous

It would be desirable to undertake research efficiently and effectively with the projects related to the Project for Clarification and Control of the Aging Mechanism (provisional name) started by the Japan Agency for Medical Research and Development (AMED) in FY2017, and the consortia, academic associations, and research institutes in Japan and overseas such as RIKEN which started aging research entitled Contribution to Solving the Problem of Super-Aging Society through Interdisciplinary Initiatives in Life Science, in FY2016.

R&D Area for the Research and Development Objective : "Understanding the crosstalk and symbiosis between the microbiome and the host organism and its applications to health and healthcare"

2. Understanding the interactions and symbiosis between the microbiome and the host organism, leading to an understanding of the mechanisms of disease onset

Program Supervisor (PS): Chihiro Sasakawa, Director, Medical Mycology Research Center (MMRC), Chiba University
Program Officer (PO): Hiroshi Ohno, Group Director, Laboratory for Intestinal Ecosystem, RIKEN Center for Integrative Medical Sciences

Outline of the Research and Development Program

In this R&D area, we aim to achieve a better understanding of the molecular mechanisms of host-microbiome interactions and symbiosis, and utilize these findings to elucidate their impact on disease onset, thereby contributing to the development of new concepts for health and healthcare through the control of the human microbiome.

Various microorganisms—bacteria, fungi, viruses—live in the parts of the human body that come into direct contact with the external environment, such as the digestive tract, skin, oral cavity, nasal cavity, respiratory organs, and reproductive organs. These microorganisms form microbiomes with different characteristics specific to each location. Research is starting to show that the microbiomes of healthy individuals differ from those in diseased individuals in a wide range of diseases and conditions, suggesting that the microbiome plays an important role in health and disease. We now hope to discover new technologies for health and healthcare, such as novel diagnostic and preventive methods that use microbiome-related biomarkers to predict disease onset; techniques for personalized medicine that use individual differences in the microbiome to predict whether an individual will be responsive to a drug or experience side effects; or functional foods and/or pharmaceuticals based on discoveries of new mechanisms of action. However, we know almost nothing about the mechanisms involved in host-microbiome interactions, symbiosis, and disease onset, including how these microbiomes are formed, what causes them to change, and what are the mechanisms by which they affect human health, disease onset, or disease progression. We need to reach a comprehensive understanding of these mechanisms if we are to develop our findings on the microbiome into technologies that can contribute to society. Because host-microbiome interactions are extremely diverse and complex, we need to ensure that the research program brings together researchers from various fields; from basic medicine and microbiology to immunology, clinical medicine, and bioinformatics.

To achieve the aim of this R&D area, we hope to gather researchers from various fields and foster their collaborative works to gain a better understanding on the mechanisms of host-microbiome interactions, symbiosis and their roles in disease onset. This should develop new strategies for health promotion and healthcare technologies by controlling the human microbiome.

Policy of the Program Supervisor and Program Officer on call for applications, selection, and project management

This aim of this R&D area is defined as understanding the molecular mechanisms of host-microbiome interactions and symbiosis and its impact on health and disease onset.

Upon recognition of the importance of microbiome on the hos physiology and pathology, we expect that the research in this R&D area will lead to the development of novel health-promoting and healthcare technologies, particularly methods that improve lifestyle habits through monitoring health status and prediction of disease onset based on examining human microbiome; health-promoting or therapeutic technologies by controlling the human microbiome; and various functional foods and pharmaceuticals based on the mechanisms of the interaction between the microbiome and the host immune system. Especially, these developments are more expected, because clinical studies on fecal microbiota transplantation (FMT) are recently underway for various diseases including pseudomembranous enteritis that is characterized as intractable diarrhea.

However, we have only just started to elucidate basic molecular mechanism how the extremely complex assembly of microbiomes and advanced organism host can form their well-coordinated interaction, so we still have a lot to learn. This R&D area will prioritize basic research to clarify the detailed mechanisms involved and to establish robust foundations from which we will be able to develop novel technologies.

To achieve this, we will assemble researchers from a wide range of fields, including basic medicine, microbiology, immunology, clinical medicine, and bioinformatics, etc., and we will define rules for the R&D area, for example on sampling methods or methodology for data collection and analysis, to ensure that the various researchers participating in this area can study and discuss in the same platform. Moreover, in order to promote collaboration within the R&D area and ensure that budgets are used effectively, the purchase of relatively expensive equipment such as next-

generation sequencers and mass spectrometers will only be approved for specific R&D programs and these programs will work as the hub laboratories for advanced analysis within the R&D area, strengthening the formation of networks across the R&D area. Through this, we all will establish virtual research sites to create new ideas in this R&D area and the researchers will work together to achieve the R&D objectives.

(1) AMED-CREST (unit type)

For this R&D area, we will accept innovative basic research proposals which will elucidate the mechanisms involved in host-microbiome interactions, symbiosis and the mechanisms behind disease onset, which will contribute to the development of novel health and healthcare technologies through the control of the human microbiome.

For example, we expect research programs to understand the mechanisms involved in microbiome formation and modification, the mechanisms through which interaction between the indigenous microbiota and the host affects host physiological function, or the mechanisms relevant to the human indigenous microbiota and disease. The indigenous microbiota to be investigated will not be only the intestinal microbiome but will also be the microbiomes present in the skin, oral cavity, nasal cavity, respiratory organs, and reproductive organs. We also welcome proposals for basic research using mouse models, and unique ideas that may help us unlock the secrets behind host-microbiome crosstalk. There is no requirement for the researchers submitting proposals to be currently involved in microbiome research. We welcome innovative new proposals from different research fields as long as they are scientifically reasonable. Although we are interested in basic research proposals, we will also focus on whether intellectual property rights can be secured for the research outcomes, because this is important when developing novel health and healthcare technologies.

In order to elucidate the extremely complex host-microbiome relationship, we expect to form a multidisciplinary research unit that encompasses basic medicine, microbiology, immunology, clinical medicine, chemical biology, systems biology, and other fields. We welcome submissions from researchers who work proactively with colleagues in other fields during the course of their research.

Purchase of relatively expensive analytical equipment such as next-generation sequencers is not permitted. Instead, coordination with site function programs and use of shared equipment at research institutes is required.

- We will select approximately 2-4 proposals for AMED-CREST this fiscal year, with a total budget of up to 390 million yen per project for R&D costs (including 90 million yen indirect costs) over the project term. Proposals for more than this limit should not be considered for approval.We will also solicit the following site function programs.

***Site Function Programs （approximately one program）**

We will adopt around one proposal as a site function program to fulfill the policy of supporting the analysis of samples in the R&D area, and promoting the cycle of collection, accumulation and use of data obtained for use in the R&D area.

Specifically, the site function program will accept samples and the like from other R&D projects within the area requiring cooperation as necessary, and provide analytical support such as sequencing nucleic acid, computational analysis and so on. Support for human metabolome analysis is not necessarily required, but it would be desirable if coordination is possible. Furthermore, in order to promote the cycle of collection, accumulation and use of research data to prevent it lying unused, the site function program is required to play a central role in promoting efficient and effective research while cooperating with public Japanese institutions such as the National Bioscience Database Center (NBDC) of the Japan Science and Technology Agency (JST).

We want specific proposals for establishing frameworks that take responsibility for the site functions. We also welcome perspectives on fostering the next generation of microbiome researchers. Development research that contributes to site functions is also possible. Another selection criteria in addition to the proposal content is the ability to conduct microbiome analysis, such as a track record of experience, know-how, owned facilities and so on related to metagenome sequencing.

In principle, concerning relatively expensive analytical equipment such as next-generation sequencers for site function programs, you will be required to make effective use of existing equipment by using shared apparatus at research institutes. Furthermore, the costs required for analysis should be borne by the requesting party, therefore it is necessary to conclude joint research agreements between research institutes and receive appropriate expenses.

Standardization of methods of microbiome analysis is important for supporting nucleic acid analysis. In this R&D area, there has been considerable discussion of important issues such as standardizing methods of microbiome analysis, with exchanges of opinion with PS, PO, advisors, related projects within AMED, industry and so on. The site function program will inherit the existing cooperative frameworks, and must promote the updating and adoption of microbiome analysis methods and information.

(2) PRIME (solo type)

The PRIME program invites proposals for unique studies that focus on individual researcher's specific fields and those in relation to the R&D areas as described in the AMED-CREST program. This R&D area relates to host-microbiome interactions, symbiosis, and mechanisms of disease onset, so we welcome proposals for challenging programs that could lead to new breakthroughs; attempts to understand the basic mechanisms from a completely new viewpoint, even if the research is already at the applied stages; and research that could develop completely new technologies that may contribute to basic research (for example, an innovative new technology that leads to a dramatic improvement in the culture of microorganisms that are difficult to grow).

We recommend proposers collaborate actively with other research groups in the same or different fields, particularly other AMED-CREST research units, for the future application of their research outcomes. Although we are looking for basic research like AMED-CREST, it is important to develop new health and healthcare technologies for the future, so another key factor will be the ability to secure intellectual property rights on the research outcomes.

Purchase of relatively expensive analytical equipment such as next-generation sequencers is not permitted. Instead, coordination with site function programs and use of shared equipment at research institutes is required.

- We will select approximately 8-10 proposals for AMED-CREST this fiscal year, with a total budget of up to 52 million yen per project for R&D costs (including 12 million yen indirect costs) over the project term. Proposals for more than this limit should not be considered for approval.

Briefing of Solicitation for this research area is planned as following date. (NOTE: only in Japanese.)
Date: April 28, (Fri.) 15:00 – 15:40
In detail, please refer "III. 2. (5) Schedule for Briefings of Solicitation."

(Reference) Research and Development Objective: “Understanding the crosstalk and symbiosis between the microbiome and host, and the applications to health and healthcare”

1. Title of the Objective

Understanding the crosstalk and symbiosis between the microbiome and host, and the applications to health and healthcare

2. Outline of the Research and Development Program

The microbiome is the term used to describe the collective entity of all the microorganisms—bacteria, fungi, parasites, and viruses—that live in the bodies of humans and other animals, in the skin or digestive tract for example, in numbers that surpass by a wide margin the number of cells making up the host organism’s body. Research has started to suggest a possible link between the microbiome and disease onset or progression, as individuals with various different diseases or conditions (such as obesity) tend to have a different microbiome to healthy individuals. Research into the microbiome is starting to gather momentum worldwide. Fecal microbiota transplantation (FMT) is another area in the spotlight; clinical studies are now underway to test whether FMT can treat various diseases, including pseudomembranous colitis that is characterized by intractable diarrhea. Research into the microbiome could lead to groundbreaking new technologies for health and healthcare, which may then be adopted in other industries such as food, cosmetics, or animal husbandry. The most pressing issue that research needs to address involves the mechanisms behind the interactions (crosstalk) and symbiosis between the microbiome and the host organism.

For this R&D objective, we aim to combine technologies from the various research and technical fields where Japan boasts expertise—such as immunology, microbial culture, metabolite analysis, model animals, or endoscopic approaches to harvesting the gut flora—and take a strategic approach to establish methods to control the microbiome. We expect this research to create value for society through longer healthy lives and optimized healthcare spending.

3. Goals to be achieved

For this R&D objective, we aim to delve into the new frontier of the microbiome with the goal of furthering our understanding of life and disease and discovering new technologies for health and healthcare based on novel concepts unlike conventional approaches. Specific goals are as follows:

(1)Develop more advanced technologies for microbiome analysis
(2)Clarify the mechanisms behind host-microbiome interactions and disease onset
(3)Develop new preventive, diagnostic, and therapeutic technologies involving the human microbiome

4. Research promotion focusing on the future development of our society

By achieving the goals set out in section 3. Goals to be achieved, we will help society achieve the following:

- We may be able to live longer healthy lives and ensure our healthcare systems are sustainable if we have a better understanding of the relationship between the host and the microbiome and how this relationship can be controlled.
- New industries may spring up if we clarify the relationship between the microbiome and healthy longevity and we apply these findings to the development of value-added foods and foods with health-promoting properties.

5. Specific examples of research

(1) More advanced technologies for microbiome analysis

We will develop more advanced cell-culture technologies, including high-throughput technologies for the simultaneous analysis of multiple microorganisms and culture techniques for microorganisms that are difficult to isolate or distinguish. We will also develop more sophisticated technologies for metabolome analysis and perform exhaustive, systematic analyses in order to select functional metabolites that play a role in host health and disease onset, from the many different types of biomolecules produced by the microbiome. In addition, we will develop more advanced technologies for microbial genome analysis to allow big-data analysis in short time frames and more accurate analysis of the microbiome. This will allow us to perform complete analyses (meta-transcriptome analysis) of the microbiome translation products. We will aggregate the data obtained and conduct system biology research that uses artificial intelligence (AI) and other techniques to clarify the extremely complex metabolic pathways of the microbiome.

(2) Understanding host-microbiome interactions and the mechanisms of disease onset

We will use analytical metabolomics to identify the biomolecules thought to affect various sites across the body and will elucidate the complex interactions, such as those between specific microbes (or microbial communities) or their metabolites and the mucosal immune systems on the body’s epithelium, by clarifying receptors, metabolic

pathways, and so on. Conventional research has mostly focused on the interactions between single microbes and the host, but we will accelerate research into the relationship between the microbiome and the host. We will also work to clarify the mechanisms of disease onset, for example by identifying the processes involved when changes in living conditions result in changes in the microbiome, which then gradually affect the living body.

(3) Discover preventive, diagnostic, and therapeutic technologies involving the human microbiome

Using the findings from the research described above, we will discover new health and healthcare technologies that involve the control of the human microbiome. Specific examples include the development of novel diagnostic methods, such as biomarkers that predict disease onset through the analysis of microbial metabolites or microbiome profiles in healthy individuals and patients, and the provision of optimal healthcare through a greater understanding of how the microbiome relates to drug/vaccine efficacy and side effects. In addition, we will identify those factors that allow us to control the microbiome and improve host health and thereby develop microbial cocktails, drugs, health foods, and other products for therapeutic and preventive healthcare.

6. Research trends in Japan and overseas

Trends in Japan

Microbiome research took off worldwide in the 1960s and scientists developed the concept of intestinal flora. Japan developed a good reputation around the world for its cutting-edge research into areas such as intestinal flora culture techniques and classification systems. Japanese scientists have continued their work in these areas, including research into microbial culture techniques, model animals, fermentation, and probiotics, with industrial researchers, particularly at dairy product manufacturers, investigating how the ingestion of dairy products, lactic-acid bacteria, and Lactobacillus bifidus can be used to regulate the gut. Now that the microbiome can be subjected to complete genome analysis, we are starting to see examples of world-class collaborative research, as well as individual investigations, into areas where Japan excels, such as immunology, microbial culture, metabolite analysis, and model animals. One start-up company, established in the US to apply the outcomes from basic research done in Japan, is drawing the attention of scientists worldwide for its work on the microbiome. Japan is also working to develop and apply basic analytical technologies to support such microbiome research.

Trends overseas

Over the past few years, there has been a rapid increase in the number of papers published in this field, following the launch of next-generation sequencers in 2005 and the resulting development and application of complete microbiome genome analysis. The US is pushing forward with microbiome analysis as a national project; in 2008 the country invested some ¥21 billion in phase 1 of the Human Microbiome Project to assemble basic data on the microbiome, including information from microbiome analysis in healthy individuals and data on the genomes of 3000 different types of microorganisms. During phase 2, which began in 2013, the US is investing a total of ¥3 trillion to research diseases related to the intestinal flora, based on findings from the phase 1 research. Europe and China began the Metagenomics of the Human Intestinal Tract (MetaHIT) project in 2008, investing around ¥2 trillion to analyze microbiomes in healthy individuals. The work from MetaHit is flowing into the successor project MetaGenoPoliS (MGPS), which began in 2013. Like the US project, the results from the forerunner project will be used for research into diseases related to intestinal bacteria and the role that food plays. FMT involves extracting liquid containing the microbiome from the stools of healthy individuals and transplantation into the intestines of patients; clinical applications have already begun and efficacy has been demonstrated in randomized comparative studies in patients with pseudomembranous enteritis and metabolic syndrome. Research is underway to identify the most effective microbe populations for FMT to make this method safer, more effective, and more socially acceptable. A number of start-up companies have been established and clinical studies have begun in the US on a microbial cocktail that includes a mix of microbes shown to be effective against disease. Big Pharma companies have also started to acquire start-up ventures. We are also starting to see research into microbiome metabolites or receptors as targets for drug discovery.

7. History of the investigations

Investigations were conducted as described below, based on the Policy on Defining Strategy Objectives (decision dated 8 June 2015 by the Council for Science and Technology, Strategic Basic Research Programs Subcommittee).

Creation of analysis materials relating to research trends in Japan and overseas through scientometric methods using the Grants-in-Aid for Scientific Research (Kakenhi) database and other sources

Using the Kakenhi database and other sources, we created analysis materials on research trends in Japan and overseas by applying scientometric methods, such as analysis of co-citation and direct citation relations for research papers.

Analysis materials used for a questionnaire-based survey of specialists to identify key research trends

The analysis materials produced were used to run a questionnaire-based survey of key research trends in the future that was submitted to each of the units at the Center for Research and Development Strategy (CRDS), the Program Directors at the Japan Agency for Medical Research and Development (AMED), and the specialists participating in the specialist network of the National Institute of Science and Technology Policy's (NISTEP) Science and Technology Foresight Center. The questionnaire responses were analyzed and "understanding the crosstalk and symbiosis between the microbiome and host and the applications to healthcare" was specified as a key research trend.

Workshops and creation of R&D objectives

A workshop was held where experts from the industries relevant to the key research trend of "understanding the crosstalk and symbiosis between the microbiome and host and the applications to healthcare" assembled to discuss key trends in Japan and overseas, the possible social and economic impact of developments in research and technology development and the possible future of society from these outcomes, and objectives that need to be achieved during the research stages. These workshop discussions were used to develop the R&D objectives.

8. Relevant descriptions included in Japanese Cabinet documents

5th Science and Technology Basic Plan (Cabinet decision dated 22 January 2016)

Chapter 3 (1) <2> i)

Japan has already become the most super-aged society in the world and we need to pursue basic scientific research to develop healthcare technologies and use these results to extend our healthy longevity and ensure the sustainability of our healthcare system. By discovering new drugs and developing medical devices and healthcare technologies in Japan, we aim to make our industries more competitive in healthcare-related fields and help support economic growth in Japan.

The Plan for Promotion of Medical Research and Development (approved by the Headquarters for Healthcare Policy, 22 July 2014)

2. 1. (5) <2>

… 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.

9. Miscellaneous

- We expect the outcomes from the research under the R&D objectives discussed here will have applications in a wide range of fields, from pharmaceuticals to medical devices, preventive healthcare, and personalized medicine. We expect this research to be developed for practical applications through tie-ups with the collaborative projects at AMED, including the Project for Drug Discovery and Development and the Japan Genomic Medicine Project.
- For the biomolecules and data (including patient information and reference information from healthy individuals) obtained during the course of the research under the R&D objectives discussed here, we expect to link up with the Life Science Database Integration Coordination Program at the Japan Science and Technology Agency (JST) (from 2011) to build the foundations, such as database population and library development, to support further development in order to make the research more efficient and effective.

R&D Area for the Research and Development Objective: Elucidation of Mechanobiological Mechanisms Leading to the Development of Innovative Medical Instruments and Technologies

3. Elucidation of Mechanobiological Mechanisms and Their Application to the Development of Innovative Medical Instruments and Technologies

Program Supervisor (PS): Masahiro Sokabe (Professor, Mechanobiology Laboratory, Nagoya University Graduate School of Medicine)
Program Officer (PO):Joji Ando (Professor, Laboratory of Biomedical Engineering, School of Medicine, Dokkyo Medical University)

Outline of the Research and Development Area

The main objective of the program is to elucidate the mechanisms by which cells and tissues sense, transduce, and respond to physical stimulations and to utilize such mechanobiologic knowledge to develop new fundamental technologies that will lead to medical applications.

In recent years it has become apparent that cells in a human body are exposed to a variety of physical forces created by the motion of skeletal muscles and organs and by blood stream, gravity, and neighboring cells (including mechanical forces created by the microenviroment around cells), and that the cells utilize such physical stimulations to control their own growth, differentiation, proliferation, death, morphogenesis, migration, etc. However, the precise molecular mechanisms remain unclear by which cells sense physical stimulations and convert them into intracellular biochemical signals and their ultimate physiological or pathological responses. In order to clarify the roles of physical stimulations in the structure and function of cells, tissues, organs, and organisms, mechanobiology has come into being as a new research field based on physics, engineering, biology, and medicine.

Elucidation of the mechanisms by which organisms sense and respond to physical stimulations has the potential to lead to breakthroughs in the effort to solve various biological and medical problems, e.g. problems concerning ordered formation of tissues during the growth and development of individuals and wound healing, and regenerative medicine. Moreover, by utilizing Japan's state of the art technologies such as bio-nano surface technology and MEMS (micro-electro-mechanical systems), it should become possible to develop new devices, e.g., devices capable of quantitatively applying and controlling physical stimulations and apparatus capable of precisely measuring biological reactions to physical stimulations.

The aim of the program is to promote mechanobiology research and develop basic techniques that will lead to innovative medical instruments and technologies so as to contribute the achievement of a society in which people are healthy and live a long life.

Policy of the Program Supervisor and Program Officer on Call for Application, Selection, and Project Management

The aim of this program is not only to identify sensor molecules involved in the recognition of physical stimuli (force, heat, electric fields, magnetic fields, etc.) and elucidate their functions, but to clarify the processes through downstream signal transduction pathways to the ultimate cellular responses. This program will also clarify the roles of physical stimulations in homeostasis and the pathogenesis of disease and will promote studies that develop novel medical instruments and technologies that will be useful in preventing and treating physical-stimulation-related diseases.

Although various treatments that use physical stimulation have been successfully applied in clinical fields, such as in the fields of wound healing, orthopedics, and rehabilitation, the mechanisms of their effects are not fully understood. Elucidation of the processes that occur between cell responses to physical stimulations and tissue and body healing would improve existing clinical treatments to be more scientific and reliable. Moreover, if mechanobiological studies identify target molecules that are specific to certain diseases, it may lead to innovative drug development.

This program promotes cooperation of mechanobiology with nanotechnology and computational science. The introduction of various technologies is desirable, including atomic force microscopy and laser tweezers that can be used to apply and precisely measure physical stimuli (minute forces, etc.), MEMS technology, nanotechnology (bio-nano-surface technology, etc.), and visualization technology (single-molecule imaging, etc.) and computer simulations that are able to analyze molecular dynamics inside cells. In order to develop fundamental techniques that make it possible to locally and quantitatively apply physical stimulations to cells and tissues and make real-time measurements of their responses, we encourage researchers to utilize various technologies originally advanced in Japan. Moreover, it is advisable to perform challenging studies that are specific to medical applications, such as development of a physical-stimulation-loading system that can be used to construct 3D-tissues from cultured cells

and the development of medical materials that are highly biocompatible and can be applied to physical stimulation-generating instruments used inside the body.

There are two types of programs in this project: an AMED-CREST (unit-type) program and a PRIME (solo-type) program. For the both types of programs, research proposals should have an effective organization of several disciplines, including physics, engineering, computer science, biology, basic medicine, clinical medicine, and so on. Communication and collaboration with researchers working in various disciplines would enable researchers to carry out fundamental research and development that should lead to the design of novel medical instruments and technologies based on advances in mechanobiology. We will plan to provide many opportunities for interaction and discussion among researchers and an environment that will foster unique ideas and collaborations. We hope all researchers will approach their studies with attention focused on future application to medical care through the duration of this project.

Example of research proposals.

1) Identification of novel molecules that sense physical stimuli (force, heat, electric fields, and magnetic fields) that are important in physiological or pathological phenomena, and elucidation of their mechanisms and functions.
2) Elucidation of intracellular signal transduction pathways (specific signaling cascades between sensors and effectors) that lead to cellular responses to physical stimulations, including physiological phenomena (cell motility, cell cycle, cell proliferation, and differentiation) or pathological phenomena (muscle atrophy, osteoporosis, and arteriosclerosis). Studies based on working hypotheses with distinct scientific evidence but not studies conducting a simple comprehensive analysis are recommended.
3) Development of experimental methods that enable the application of quantitative, noninvasive forces to intracellular molecules and organelles, intercellular junctions, and cell-matrix adhesion sites and of quantitative, real-time measurements of stresses induced by physical stimuli.
4) Experimental and computer simulation studies that elucidate the behavior of cell groups in development, regeneration, wound healing, etc. from the aspect of the mechanisms of cell motility and proliferation and of cell to cell or cell to matrix interactions.
5) Elucidation of the therapeutic mechanisms of physical exercise and physical therapies and their application to the development of basic technologies that will be useful in providing medical care.

(1) AMED-CREST (unit-type)

The AMED-CREST program invites proposals that will promote basic research in the field of mechanobiology that integrates a variety of disciplines, including biophysics, engineering, biology, and basic and clinical medicine, and will lead to the development of innovative medical instruments and technologies that apply physical stimulations. A representative proposer should make a team with other researchers to conduct studies on the mechanisms of cell and tissue sensing, transduction, and response to physical stimulations and to apply advanced nano-device technology as a means of connecting the new knowledge obtained from the above-described studies to the development of innovative medical instruments and technology. The unit should be well organized so that efficient synergistic effects among different disciplines can be produced.

We also welcome proposals for studies that will clarify the roles of physical stimulations in the pathogenesis, and cure of diseases and exploit effective treatment methods from a mechanobiology standpoint.

○We will select approximately 2-4 proposals for AMED-CREST this fiscal year, with a total budget of up to 390 million yen per project for R&D costs (including 90 million yen indirect costs) over the project term. Proposals for more than this limit should not be considered for approval.

(2) PRIME (solo-type)

The PRIME program invites proposals for unique studies that focus on individual researcher's specialty and relate to the same research and development areas as described in the AMED-CREST program. We welcome proposals for breakthrough studies in the basic and technological areas related to mechanobiology, even if the study is not in the application phase, and we also welcome proposals for studies that investigate the molecular mechanisms of mechanobiolgic therapies from a novel viewpoint, even if the therapies are already being applied. We recommend proposers to perform active collaborations with other researchers for the future application of results of their studies.

○We will select approximately 8-10 proposals for AMED-CREST this fiscal year, with a total budget of up to 52 million yen per project for R&D costs (including 12 million yen indirect costs) over the project term. Proposals for more than this limit should not be considered for approval.

Points to consider in calls for research proposals in FY2017, for both AMED-CREST and PRIME research proposals

This fiscal year, as well as the proposals rooted in the aims of the research and development areas, we welcome proposals on basic research and development that investigate from mechanobiological perspective the mechanisms of how effects are exhibited in the healthcare technologies and medical devices already confirmed as effective in the clinical setting. We also hope to receive high quality research proposals with keywords such as nano-bio surface, MEMs (micro-electro-mechanical systems), bio-imaging, and mechanotransduction. In addition to the systems needed to pursue the basic science of mechanobiology, we encourage researchers to develop systems that can incorporate clinical perspectives with a view to clinical applications, develop international collaborations, and facilitate rapid results through the sharing of equipment for example.

Briefing of Solicitation for this research area is planned as following date. (NOTE: only in Japanese.)
Date: April 28, (Fri.) 13:40 – 14:10
In detail, please refer "III. 2. (5) Schedule for Briefings of Solicitation."

(Reference) Research and Development Objective: "Elucidation of Mechanobiological Mechanisms Leading to the Development of Innovative Medical Instruments and Technologies"

1. Title of the Objective

Elucidation of Mechanobiological Mechanisms Leading to the Development of Innovative Medical Instruments and Technologies

2. Outline of the Research and Development Program

The fact that living organisms are constantly exposed to physical stimuli e.g. gravity, to which they constantly adapt, is clear, as exemplified by substantial loss of muscle mass and bone density after space flight or disuse atrophy after prolonged immobility. Mechanobiology is an emerging research field aiming to elucidate how physical stimuli are detected by molecule, intracellular organelle, cells and tissues, and elucidate the biological response to and regulatory mechanism against these stimuli. In recent years, we have seen the potential to apply physical stimuli for medical use, e.g. developing new therapeutic modality using an angiogenic response to sonic waves.

The objective of this R&D program is to create innovative medical equipment and technology and achieve a healthy and long-life society by fusing cutting-edge in-depth measurement/control technologies, of which our country is proud, by elucidating mechanisms to receive and regulate physical stimuli and the intracellular signal transduction mechanism that takes place after physical stimuli are received, and thereafter by selecting and controlling optimal physical stimulation which can induce target response.

3. Goals to be Achieved

This R&D program aims to create innovative medical equipment and technology by elucidating the mechanobiological mechanism. We specifically target the following objectives:

① Creation of research seeds for novel medical applications to certain diseases, based on elucidating mechanism of sensing regulation and response against physical stimulation.

② Creation of fundamental technology that contributes to developing and optimizing a physical stimuli-generating device for medical applications by utilizing bio-nano interface technology.

4. Research promotion focusing on the future development of our society

This program will contribute to realizing a society as described in the following after achieving the actions mentioned in the above "3. Goals to be achieved":

○ A society where safe and cost-effective medical services, which further extend the healthy lifespan, are realized after developing advanced medical technologies, including innovative medical equipment actively utilizing physical stimuli, effective disease prevention, preemptive medicines and a medical rehabilitation. via an elucidated mechanobiological mechanism.

5. Specific examples of research

① Creation of research seeds for novel medical applications to certain diseases, based on elucidating mechanism of sensing regulation and response against physical stimulation.

We perform comprehensive analysis such as transcriptome and proteome to elucidate intra- and intercellular response mechanisms, and to identify membrane proteins involved in sensing of physical stimuli and proteins constituting cytoskeleton. We also engage in research to elucidate the regulatory system caused by physical stimuli-induced structural changes in proteins which constitute cell membranes and subcellular organelle. We further extend our cell-based knowledge to the level of tissues and organs, and engage in R&D to create innovative medical equipment and medical technologies for newly indicated diseases, based on an elucidated mechanobiological mechanism. Our R&D works include, for example, to clarify a healing mechanism for bone fractures enhanced by physical stimuli, angiogenetic mechanism by sonic waves, mechanism of accelerated wound healing by pressure, and mechanism of hyperthermic treatment for cancer.

② Creation of fundamental technology that contributes to developing and optimizing a physical stimuli-generating device for medical applications by utilizing bio-nano interface technology.

We develop a method to generate and control appropriate physical stimuli that induce the targeted vital phenomenon, after developing technology to control focal stimulation on a nano scale and a measuring technology to perform a quantitative assessment of the contractile force generated by cells and intra-tissue stress (strain) distribution. We also develop fundamental technology which facilitates the development of a mechanical stimulation load system for three-dimensional cell and tissue culture, an in-depth analysis such as visualization technology by live cell imaging to elucidate the detection and response mechanism against physical stimuli and

fundamental technology for medical applications, including the development of highly biocompatible medical materials, which induce in-vivo physical stimuli.

6. Research trends in Japan and overseas Trends in Japan

Mechanobiology has steadily been developed as a new field of science and technology in our country as it was promoted as a project under the Grants-in-Aid for Scientific Research (Grant-in-Aid for Specially Promoted Research), selected as an International Cooperative Research Project (ICORP) promoted by the Japan Science and Technology Agency, and selected in the List of Disciplines and Research Fields with a Time Limit set up for the Grants-in-Aid for Scientific Research in FY2012. The area of applied research includes active research for the musculoskeletal and circulatory systems, and a whole series of remarkable accomplishments has been made in areas of wound healing and reproductive medicine. The number of research papers published in our country ranks second after the U.S. and Japan occupies about 6% of all papers in this field as the author's native country. However, the number of papers published from 2012 onward has remained stagnant and we must promote the research work from a strategic perspective. Mechanobiology is a discipline which fuses together physics/engineering and medical science/biology. Although our country has a competitive advantage in each academic area, we lack a viewpoint from an interdisciplinary perspective and the opportunities for communication among researchers in different disciplines are currently insufficient compared to other countries.

Trends Oversea

Although the U.S.A. overwhelmingly dominates with a share that comprises approximately half of global publishment, each country other than the U.S. shares 10% or less and the competition is intense. The National Institute of Biomedical Imaging and Bioengineering was established as part of the National Institute of Health (NIH) in the U.S. in 2000 and the National Science Foundation (NSF) is pushing its support for fundamental research by increasing its resource distribution to biomechanics and mechanobiology. Internationally, although few institutions are dedicated to mechanobiology, major U.S. universities have established many biomedical engineering research facilities, and their educational research activities in mechanobiology are actively being promoted. Also, in Asia, the Mechanobiology Institute (MBI) was established in Singapore in 2009. MBI recruited researchers through international solicitation from the world, including a professor from Columbia University to promote research work.

7. Sequence of Selection

The following reviews were conducted pursuant to the report of "Review Session on the Current State of Strategic Basic Research (June 27, 2014)".

(Preparing Domestic and Foreign Research Trend Analysis Using a Science Map and Database of Grants-in-Aid for Scientific Research)

Domestic and Foreign Research Trend Analysis was prepared using information provided in the "Science Map 2012 & 2010" (National Institute of Science and Technology Policy, July 31, 2014) and Database of Grants-in-Aid for Scientific Research.

(Conducting Survey of Experts Using the Above Analysis and Preparation of a Survey Report on Noteworthy Research Trends)

A survey of experts who participated in the expert network of the "Center for Research and Development Strategy of Japan Science and Technology Agency" and the "Center for Research of Science and Technology Trends of the National Institute of Science and Technology Policy" was conducted to question noteworthy future research trends using prepared analysis data. Subsequently, following analysis of the survey result, we identified both "Development of the Next-Generation Medical Technology Based on Mechanobiology" and "Research and Development of Fabrication Technology for Interactive Bio-Interface" as noteworthy research trends.

(Holding the Workshops and Preparing the R&D Objectives)

We hosted workshops for each theme; inviting experts from industry and academia involved in the "Development of Next-Generation Medical Technology Based on Mechanobiology" and "Research and Development of Fabrication Technology for Interactive Bio-Interface" as noteworthy research trends, where all experts met and discussed the key domestic and foreign trends, socioeconomic impacts caused by progress in the research and technical developments, resulting social image in future and objectives to be achieved during the research period. The R&D objectives were prepared based on discussions at each workshop.

8. Relevant Descriptions Provided in Documents and Others Approved by the Japanese Cabinet

"Plan to Promote Medical Research and Development" (approved by the Headquarters for Healthcare Policy, July 22, 2014)

Ⅰ.1.(1) ③

It is expected that our country, as a scientific and technological powerhouse, should aim to become such a country where leading global medicine and medical technology are developed and can be promptly offered to the public by maximizing not only cutting-edge medical technology, e.g. genomic analysis or regenerative medicine using stem cells, including iPS cells, but also significant problem-solving skills available in engineering, material science and manufacturing industries of our country.

"The 4th Basic Plan for Science and Technology" (approved by the Japanese Cabinet, August 19, 2011)
Ⅱ. 4. (1)

This plan is to materialize sustainable national growth and social development by creating and promoting medical, nursing and health services. Furthermore we target international contributions by developing medicines and medical equipment to deal with the aging society which developed countries leverage to promptly confront and with diseases which are extensively spread in developing countries.

"Comprehensive Strategy on Science, Technology and Innovation 2014" (approved by the Japanese cabinet, June 24, 2014)
Chapter 2, Section 2 3. (4) ①

Device systems developed differently from conventional approaches, including the "Nano Bio-Device System", which is a bio-device allowing in-vivo interactions with living organisms, come to the fore. Efforts to use these innovative devices for next-generation device systems are expected to generate major interdisciplinary ripple effects.

9. Miscellaneous

· The research outcome to be produced by the objective of this R&D program is expected to be applied directly to medical equipment, directly allowing biological responses to physical stimuli to be regulated. To meet this expectation, further efforts to bridge research outcomes under the objective of this R&D program with practical applications are expected in the cooperative project featuring an "All-Japan Effort to develop Medical Equipment" or "Project of Innovation of Creative Center for Novel Medical Technology" of the Japan Agency for Medical Research and Development.

R&D Area for Research and Development Objective: Comprehensive Elucidation of Functional Lipid Which Contributes to Breakthrough Medicines

4. Studies on Specific Activities and Functions of Lipid Molecules to Develop Innovative Medical Technologies

Program Supervisor (PS): Shinji Yokoyama (Director, Nutritional Health Science Research Center, and Professor, College of Bioscience and Biotechnology, Chubu University)
Program Officer (PO): Yasuyuki Igarashi (Professor, Faculty of Advanced Life Science, Hokkaido University)

Outline of Research and Development Area

Lipids carry fundamental functions in living organisms as major components of biomembranes and energy-storage molecules. Numbers of their derivatives also play specific roles in regulating metabolism, immunity/inflammation, reproduction, circulation, neural network, etc, and are involved in pathogenesis of various disorders and diseases related to these systems. The objective of this research and development program is to investigate novel biological functions of lipids and develop new technologies for their analysis, to elucidate molecular mechanism of lipid-associated various diseases, and finally to exploit novel developmental seeds for compounds and technologies to overcome these diseases, i.e. chemical compounds relevant to pre-clinical stage, target materials and reactions promising medical application in near future, or innovative diagnostic methods that may construct new clinical benefits, etc.

Lipid research has advanced along with numbers of discovery of new biological activities and exploitation of new analytic technologies. Therefore, more innovative research and exploitation should also be necessary in order to accomplish the goal of this program and initiatively dispatch the novel results toward the world. It should be also important to gather ideas of researchers in various different fields and disciplines, such as the scientists in clinical medicine, pharmaceutical sciences, synthetic chemistry, biophysics and bioengineering, and information engineering, as well as those in lipid biology and biochemistry who have carried mainstream of lipid research. Broad viewpoints based on our interdisciplinary research team works will be indispensable for advancement of research and development in lipid research field to strengthen our international competitiveness.

We would like the program members to conduct their researches with practical translational outputs always in their mind. However, it does not necessarily mean that all the members are obliged to produce practical seeds within the term. We consider it is also important to promote fundamental basic studies that would possibly become the basis for generation of innovative technologies, diagnostics, and medicines only in not-remote future, for development and enforcement of international competitiveness of our lipid research. The research field of biological activities of lipids is continuously expanding, and this project is expected to lead the world in innovative and explorative research in this field.

Because of expected medical application, target lipids are primarily set as the molecules originating in mammalian cells. However, the molecules closely related to human disorders and of nutritional importance may be included, such as omega-3 fatty acids and ceramide.

Policy of the Program Supervisor and Program Officer on Call for Application, Selection, and Project Management

The mission of this program is to elucidate molecular mechanism of pathogenesis that involves biological activity of lipid molecules, and to explore practical translational seeds for medical application based on robust molecular evidence. We intend to target the diseases not only those of great importance in public health in Japan, but also relatively rare but “hard-to-cure” diseases. Examples may be listed below for the potential research subjects.

- Molecular mechanisms for actions of specific lipid mediators/receptors, molecules involved in lipid metabolisms/dynamics in living organisms, and their application to drug development
- Exploitation of non-invasive imaging technologies for diagnosis of disorders and diseases by using synthetic lipid probes
- Chemical synthesis of biologically active lipid derivatives and their application to drug development
- Lipid-protein interactions and their biological significance, development of novel biophysical methods for analyzing those

We also welcome highly original ideas about the lipids of biological activity and functions. We don’t necessarily require preliminary ongoing lipid research activity for the proposals. Innovative and rational proposals from different disciplines shall be highly appreciated.

(1) AMED-CREST (unit-type)

The objective of this program is to create practical translational seeds for medical application. The program is thus expected to contribute and benefit to publish health of peoples in Japan by returning the results our research activities on biological activity of lipid molecules to clinical application. In this context, we expect proposals setting clearly stated goal for every year, the concrete target to be achieved at the endpoint, and description of possible applications in the near future, but not a proposal expecting serendipity. In the process of selection, we consider it important whether the outcome of the project potentially acquires intellectual property rights. On the other hand, we would not like to see possibility of long-term down falling of lipid research here in a few decades by promoting only the projects with easy-to-accomplish goals. Thus, it is also our mission to encourage sprouting studies that would become the cores of lipid research field in the future, raise world-class young medical investigators, and thereby widen and strengthen the foundation of lipid research area in Japan.

The lipid research area is highly competitive worldwide, so that we need steady progress of research without delay. It is therefore necessary to organize a research unit to working efficiently throughout the term of the program. Clinical scientists and industrial investigators are recruited to your team if necessary. They of course can apply to this area as a unit leader. We expect strong proposals by the units which exhibits high competitiveness in the world and insures intellectual property rights.

Active collaboration among the teams in the program will be encouraged. In particular, cooperation should be helpful to verify the validities of novel technologies developed by PRIME researchers.

○We will select approximately 2-4 proposals for AMED-CREST this fiscal year, with a total budget of up to 390 million yen per project for R&D costs (including 90 million yen indirect costs) over the project term. Proposals for more than this limit should not be considered for approval.

○This program also intends to support construction and maintenance of a lipid database which should be of benefit to lipid investigators as well as those in different disciplines. We should like the members to help and cooperate the database activity.

(2) PRIME (solo-type)

We would like to invite proposals on development of technologies and studies for biological activity of lipid molecules based on novel viewpoints and innovational approaches, as well as those described above. In technological development, current or ongoing precedent application studies for lipids are not prerequisite for application and selection. We welcome those proposals of high potentials of theoretical application to the fields of lipid research, biological analysis, and thereby promising innovative results, such as application of bioinformatic technologies, chemical synthesis of unique lipid derivatives or lipid-probes for visualizing biologically active lipids in living cells and tissues, innovative physicochemical methods for lipid analysis and imaging, etc. Innovative approaches to isolate novel biologically active lipids and to determine their structures are also appreciated.

Many of the research examples above are fundamental, and practical translational seeds may not be expected at the endpoint of the program. However, this program is to contribute to research and development in medical application and aim at scientific and social innovation. Therefore, we ask the investigators to keep social return of the results in their mind, and not to fall in self-satisfaction or self-interest. Even though PRIME investigators are expected to conduct the research independently, they are encourage to collaborate with other investigators in the program, especially with those of units of AMED-CREST, when the expected research and development results are obtained for medical application. It is indispensable to acquire intellectual property rights for the research outcome.

This program will be organized as a virtual network institute. We hope that the program will become a good opportunity for the investigators to communication with those in other different disciplines, to contribute to advance of research activity in lipid field, and to expand their research activity.

○We will select approximately 8-10 proposals for AMED-CREST this fiscal year, with a total budget of up to 52 million yen per project for R&D costs (including 12 million yen indirect costs) over the project term. Proposals for more than this limit should not be considered for approval.

○This program also intends to support construction and maintenance of a lipid database which should be of benefit to lipid investigators as well as those in different disciplines. We should like the members to help and cooperate the database activity.

Briefing of Solicitation for this research area is planned as following date. (NOTE: only in Japanese.)
Date: April 28, (Fri.) 15:40 – 16:10
In detail, please refer “III. 2. (5) Schedule for Briefings of Solicitation.”

(Reference) Research and Development Objective: ”Comprehensive Elucidation of Functional Lipid Which Contributes to Breakthrough Medicines”

1. Title of the Objective

Comprehensive Elucidation of Functional Lipid Which Contributes to Breakthrough Medicines

2. Outline of the Research and Development Program

Functional lipids, which regulate various biological phenomena including human diseases, are the products of metabolic reactions involving membrane phospholipids and others, and comprise important molecular groups for living organisms, including lipid mediators to induce cellular response and membrane lipids to regulate membrane protein. Due to the development of mass spectrometric technology infinitesimal quantities of lipid metabolite can now be detected. Progress in elucidating new functional lipids and metabolic pathways of these lipids is expected to contribute to developing innovative drugs as a promising drug candidate.

However, since an experimental technique for hydrophobic lipid molecules exhibits low compatibility with research methodologies in life science for hydrophilic compounds such as proteins, DNA, etc, difficulty in measuring comprehensive real-time lipid analysis and manipulation in a living organism, lipid analysis for extensive disease research has yet to be performed, hence the increasingly urgent need for a technical breakthrough becomes apparent.

Accordingly, in this R&D program, utilizing accumulated national research findings for functional lipids and fundamental technology for drug discovery, we aim to create innovative practical seeds such as drug discoveries by breaking lipid-specific technical barriers as mentioned above and by elucidating disease mechanisms focusing on functional lipids for extensive disease research.

3. Goals to be achieved

Under the objective of this R&D program, we conduct the required technological developments and ultimately aim to create new practical seeds, which contribute to overcoming diseases, including innovative medicines and diagnostic markers, after elucidating various functional lipid-mediated disease mechanisms. Specifically we aim to accomplish ③ while engaged in technical development for ① and ②.

①Development of innovative technology contributing to ultrasensitive, highly precise next-generation lipid analysis.
②Development of control technology to manipulate functional lipids freely.
③Elucidation of molecular mechanisms for various diseases by focusing on functional lipids

4. Research promotion focusing on the future development of our society

Contributing to realizing a society as described in the following after completing the actions mentioned in the above “3. Goals to be achieved”:

- ○ A society where healthy longevity is realized by elucidating the mechanism of functional lipids and their application to drug discoveries, where functional lipids are, as pointed out, involved in various diseases, including those with no established effective medical treatments (unmet medical needs) e.g. immune, reproductive and metabolic disorders, cardiovascular diseases, inflammatory diseases including cancer and neuropsychiatric disorders.
- ○ A society where the burden of soaring medical costs is reduced by developing low molecular weight drugs, which are advantageous from a health economic perspective, including production/storage cost, by utilizing low molecular weight functional lipids, which can themselves be deployed as seed compounds for drug discovery research and relatively easily synthesized for mimicking or inhibiting its activities.
- ○ A society where diseases that influence QOL e.g. infertility, atopic dermatitis and bronchial asthma, are overcome by drug discoveries from functional lipids and the quality of life for women and children is improved, despite our aging society and declining birth rate.

5. Specific Examples of Research

① Development of innovative technology contributing to ultrasensitive, highly precise next-generation lipid analysis.

In order to find novel functional lipids, to identify precise location of production/action of functional lipids, and to clarify molecular mechanism of functional lipids, other than mass spectrometry (MS) technologies, we also develop imaging technologies using CT and PET, and data-driven lipidomics analytical technologies using non-target MS. We develop innovative analytical technologies realizing three-dimensional and real-time analysis, while also incorporating information science methods.

② Development of control technology to freely manipulate functional lipids

Since technologies for dynamic and functional regulation of functional lipids themselves are required, as well as the above microenvironment analytical technology to elucidate the physiological function of newly identified functional lipids in recent years, whose production amount in a living organism is infinitesimal, and are thought to act microlocally despite the fact its activity is powerful, we develop fundamental technology for free manipulation of lipids by utilizing chemical biology and biophysical methods to characterize lipid–protein interactions as well as conventional genetic methods.

③ Elucidation of molecular mechanisms for various diseases by focusing on functional lipids

We contribute to developing innovative practical seeds including targets for drug discovery and diagnostic markers, by promoting research for functional lipid-mediated disease mechanisms by utilizing innovative technologies developed as specified herein and elucidating mechanisms of various diseases by focusing on functional lipids, in particular, including new lipid molecules.

6. Research trends in Japan and overseas

Trends in Japan

The level of lipid research in Japan has been high and Japanese researchers have produced significant results, including identification and molecular cloning of many receptors and synthases for so-called first generation mediators e.g. prostaglandins and leukotrienes. Today, the number of research papers published in our country still ranks next to the U.S. thanks to the discovery of second-generation lipid mediators and elucidation of their significance. Contributions by Japanese enterprises are also highly outstanding, reflected in the active academic-industrial alliance, the establishment of a lipid mediator-related compound library and the fact that lipid mediator-related medicines are being marketed. Furthermore, our country has a competitive advantage based on a technological background of mass spectrometry, which has fueled the progress of research on functional lipids in both academic and industrial fields and been globally acclaimed. Additionally "The Japanese Conference on the Biochemistry of Lipids", established nationally in 1961, has maintained a lead in global lipid research because, for instance, it kick-started the "Lipid Bank" database ahead of foreign countries in 1989 and boosted the importance of lipids as a specific research field.

On the other hand, it becomes rather difficult for anyone to analyze lipids casually like genetic analysis, including microarray and sequence analyses; we are concerned at fixing research participatants.

Trends Oversea

Regarding lipid research, a research hub featuring the participation of multiple institutes, "LIPID MAPS", started in the U.S. in 2003 and has enjoyed continuous support to date from many participating research groups and huge funding from the National Institutes of Health (NIH). Currently, although "LIPID MAPS", prioritizes improvements in analytical equipment and the analysis and determination of lipid metabolic pathways overall and is not organized to search the mechanisms of functional lipids, the research focus is expected to shift to the functional analysis of lipid molecules that were newly discovered in the course of identifying metabolic pathways and metabolite and database construction. Also in Europe, "ELIfe" as the 6th Framework Program started in 2005 and research support in this area has continued in "LipidomicNet" as the 7th Framework Program. While each country actively promotes research activity in the long term, the competitive advantage of functional lipid research in our country has been almost eliminated.

Moreover, in the field of mass spectrometry techniques, Germany and the U.S., which long had a competitive edge in the iron and steel industry, moved in the area of biology and are competing with our country, while the European group, including the Netherlands, Sweden and Belgium, are actively promoting research. Developing countries e.g. China and Singapore procured large-scale equipment and have started full-scale research. Accordingly, massive efforts made by emerging countries in research to catch up are gradually gaining momentum, resembling the scene that we saw previously in the field of genome analysis.

7. Sequence of Selection

The following reviews were conducted pursuant to the "Review Session on the Current State of Strategic Basic Research (June 27, 2014)":

(Preparing Domestic and Foreign Research Trend Analysis Using a Science Map and Database of Grants-in-Aid for Scientific Research)

Domestic and Foreign Research Trend Analysis was prepared using information provided in the "Science Map 2012 & 2010" (National Institute of Science and Technology Policy, July 31, 2014) and Database of Grants-in-Aid for Scientific Research.

(Conducting a Survey of Experts Using the Above Analysis and Preparation of a Survey Report on Noteworthy Research Trends)

A survey of experts who participated in the expert network of the "Center for Research and Development Strategy of Japan Science and Technology Agency" and the "Center for Research of Science and Technology Trends of the National Institute of Science and Technology Policy" was conducted to question noteworthy future research trends in future using prepared analysis data. Subsequently, following analysis of the survey result, we identified "Elucidating the Function of Bioactive Lipids" as a noteworthy future research trend.

(Holding the Workshops and Preparing the R&D Objectives)

We hosted a workshop, inviting industrial and academic experts involved in "Elucidating the Function of Bioactive Lipids" as a noteworthy research trend, where all experts met and discussed particularly remarkable domestic and foreign trends, socioeconomic impacts caused by research progress and technical developments, the resulting social image in future and objectives to be achieved during the research period. The R&D objective was prepared based on the discussions held at the workshop.

8. Relevant Descriptions Provided in Documents and Others Approved by the Japanese Cabinet

"Plan to Promote Medical Research and Development" (approved by the Headquarters for Healthcare Policy, July 22, 2014)

Ⅰ.1.(1) ②

We target a society where the development of new medicines, diagnostic/treatment methods and medical equipment are promoted (*snip*) to combat various diseases e.g. circulatory disease including strokes, which ranks high in the category of national medical expenditure per disease and mortality in our country, (*snip*), diseases among children, who will be the backbone of the next generation and diseases originating in the perinatal period, infertility (*snip*), hepatitis, which is the most prevalent infectious disease in our country, immune-allergic disorders which reduce QOL for the long time, diseases involving chronic pain, rare diseases, refractory diseases, (*snip*), health problems endemic to females and (*snip*) .

"The 4th Basic Plan for Science and Technology" (approved by the Japanese Cabinet, August 19, 2011)

Ⅲ. 2. (2)

To create a new industrial fundamentals, we need to promote R&D at the highest level, achieving a massive global ripple effect in the fundamental area common to many industries and further enhance our industrial competitiveness.

9. Miscellaneous

- Regarding Strategic Objective 2013, "Creation of Core Technologies for Early-Stage Drug Discovery through the Investigation of Disease-Specific Profiles of Biomolecules" (Hereinafter, "Metabolism"), we understood disease pathophysiology by selecting in-vivo compounds, including functional lipids and have worked to develop the fungamental technology for drug discovery. Conversely, to discover practical seeds under the objective of this R&D program, the outcomes achieved by this "metabolism" are expected to be utilized as fundamental knowledge and linked with a research agenda for "metabolism".
- Through the objective of this R&D program, we expect lipids to become a wide open target in the life science field. We expect researchers to participate in wide-ranging fields to achieve unprecedented interactions between different disciplines, anticipating new findings produced through lipid analysis by disease researchers from different disciplines or lipid research improvement leveraging new techniques.
- We expect research results under the objective of this R&D program to contribute directly to drug discovery research. Actually there is an instance where the research outcome on functional lipids became a candidate for financial support as a academia drug discovery seed within the framework of the drug discovery support network and we anticipate that outcomes by achieving the objective of this R&D program will be translated into research for practical applications, subject to appropriate support from the Japan Agency for Medical Research and Development.

Japan Agency for Medical Research and Development

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