FY2019

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

Application Guidelines

April 2019

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

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Ⅰ. Introduction

This “Application Guidelines” is regarding R&D projects being solicited for FY 2019 under Advanced Research and Development Programs for Medical Innovation (AMED-CREST, PRIME), 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 at 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 (innovation), 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 incubation-type (LEAP)*. For AMED-CREST and PRIME, AMED specifies the R&D pursuit areas and the Program Supervisors (PS) and Program Officers (PO) for leading the research under “for leading the research 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 an 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) led by an 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 an individual R&D PI.

* LEAP targets swift commercialization of research results that are promising but where the risk of development is difficult for companies to evaluate. LEAP is not included in this round of solicitation.

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. Global competition is becoming ever fiercer 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 present day frameworks. Program Supervisors, Program Officers, and other advisers provide advice in order to not only realize the proposed R&D concepts but also develop medical applications for the research results. Moreover, the R&D fields in the program are currently organized as a collaborative system that goes beyond the bounds of ordinary scientific societies in order to attain R&D objectives. 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 these projects human resources responsible for the next generation will be nurtured. 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 young researchers will propose projects and join in the program, making great strides forward to become leading figures in their R&D areas.

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

2. Program Structure

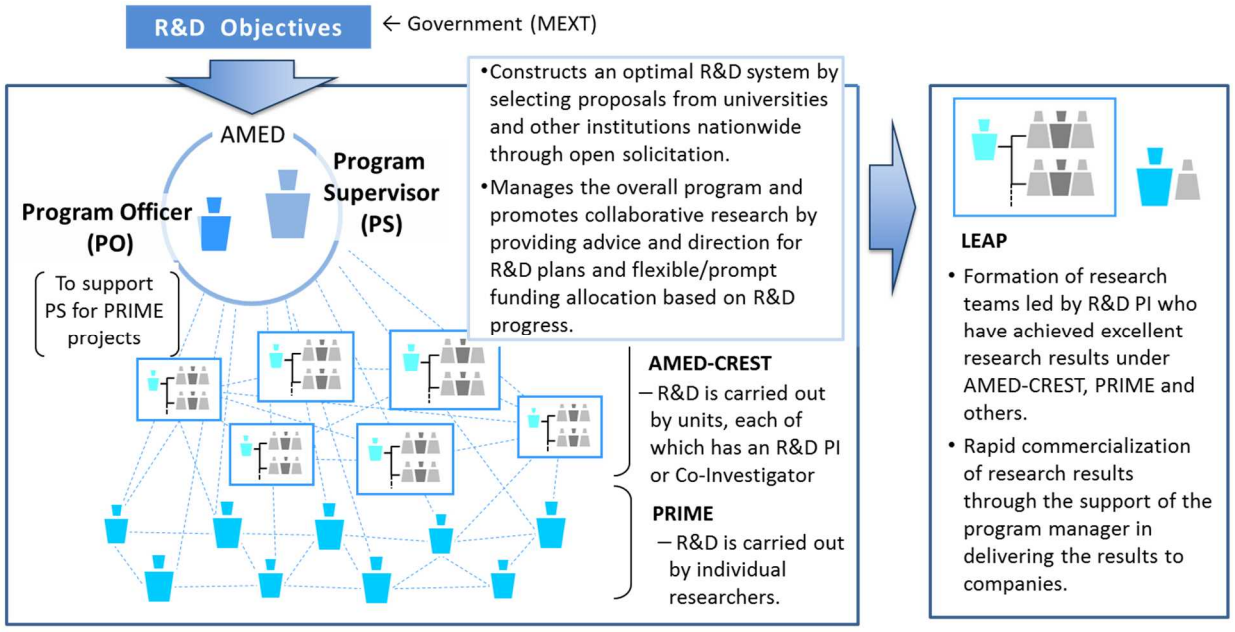
(1) Program Implementation System

In accordance with the "Plan for Promotion of Medical Research and Development*", a Program Supervisor and Program Officer 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, R&D plans may be revised or projects cancelled (including early conclusion of projects due to achievement of R&D plans) as deemed necessary.

To accomplish the R&D objectives designated by Japan's Ministry of Education, Culture, Sports, Science and Technology (MEXT), the PS and PO construct a time-limited system for conducting R&D by organizing an R&D area, assembling an optimal mix of researchers and research projects from existing organizations/institutions — namely industry, academia, and government—and oversee work in the R&D area with the cooperation of R&D Area Advisers and others. The R&D PI for AMED-CREST receives 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 and the management policies of the PS and PO, while actively building and utilizing personal networks through dialog with R&D Area Advisers and others, coordination with participating researchers, and connections with others both in Japan and overseas.

* http://www.kantei.go.jp/jp/singi/kenkouiryou/senryaku/suishinplan_henkou.pdf
* http://www.kantei.go.jp/jp/singi/kenkouiryou/en/pdf/2017_plan.pdf



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

The general 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. Please refer to Chapter III and XI for further details.

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

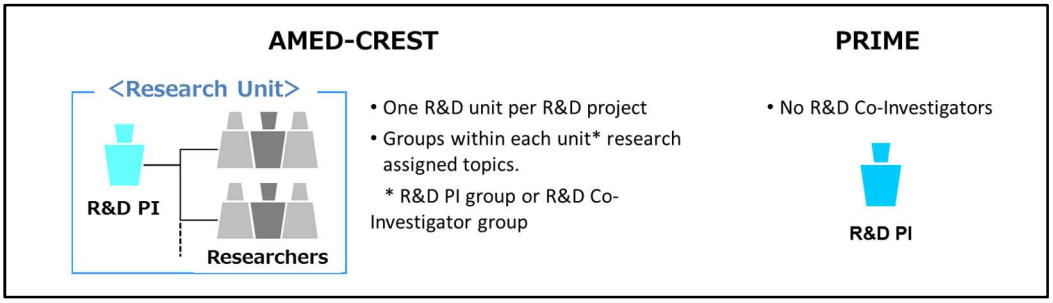
Under contract R&D agreements, AMED generally pays research institutions a separate amount for overheads (indirect costs) of up to 30% of R&D costs (direct costs).

(3) R&D Unit Organization

(a) For AMED-CREST, the R&D PI can bring multiple Co-Investigators from industry, academia, and government together optimally in a unit with the aim of realizing the R&D PI's proposed R&D 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 objectives for the overall R&D area while bearing full responsibility for the R&D project which he/she is leading. Please refer to Chapter II. 2. for further requirement details.

(b) 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 objectives and management policies of the PS and PO. Please note that Co-investigators cannot be assigned to PRIME R&D projects.

*The R&D PI who participates in the program will need to actively create and make use of networks to achieve cooperation among participating researchers and with entities both in Japan and overseas. To this end, the PI should plan and hold R&D area meetings, academic symposiums, and other events to build an R&D area network.



(4) Roles, etc. of Principal Institutions and Subsidiary Institutions

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

1) "Principal Institution" refers to the research institute with which the R&D Principal Investigator (PI) is affiliated and that is their main place of research;[1] which has concluded a direct contracted R&D agreement with AMED;[2] and which is the research institute, etc., in Japan referred to in the next item "II. Application Requirements 1. Eligible Applicants".

2) "Subsidiary Institution" refers to a research institute, etc. other than the Principal Institution with which a Co-Investigator is affiliated and that is their main place of research[1] and which has concluded a subcontracted R&D agreement with the Principal Institution.

3) "PI" refers to a researcher (one person) who is affiliated with the Principal Institution and who has 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 during the implementation period.

4) "Co-Investigator" refers to a researcher who is affiliated the Principal Institution or a Subsidiary Institution and who has the capability to share implementation of R&D items with the PI and take responsibility for carry out the relevant R&D items.

5) "Representative Investigator" refers to either the PI or the Co-Investigator affiliated with the Principal Institution or a Subsidiary Institution who is the representative researcher (one person) for the relevant research institution. (e.g.: the PI is the R&D Representative for the Principal Institution.)

[1] If the affiliate institution and the main place of research differ, please contact us.

[2] 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 an 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

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 that is their main place of research[1], 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)–(h) below.
- (a) National facility or other organization[2] (limited to institutions/facilities where the PI is employed in an educational position, research position, medical care position[3], welfare service position[3], or designated position[3], 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) Non-profit, charitable technology research associations[4]
- (h) Other institution deemed appropriate by the President of AMED.

[1] If the affiliate institution and the main place of research differ, please contact us.
[2] 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
[3] Limited to persons affiliated with a hospital or institution that conducts research.
[4] With regard to technologies used in industrial activities, mutual associations providing finance, human resources, and facilities in which the association members autonomously conduct joint 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 support researchers in relation to this program.

In only PRIME, a researcher who is not affiliated with a designated research institute or is affiliated with a research institute outside of Japan can apply for this program, if they are able to become affiliated with a research institute in Japan and create a system for conducting research by October 1 2019. However, in the case that the above conditions are not met by October 1 2019, even though the researcher was selected as a PI, as a general rule the decision to adopt the R&D project shall be cancelled. The applicant's acceptance status may be checked during the selection process.

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 an R&D Project

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

(1) An R&D unit is the optimal organizational approach for pursuing the R&D initiatives of the applicant.

(2) 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.

(3) The Principal Institution must conclude a subcontracted R&D agreement with the Subsidiary Institution appropriately.

(4) 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 an R&D Co-Investigator 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 the approval of the Program Supervisor).*
- The overseas research institution is required to transfer, free of charge, intellectual property rights to the principal institution. (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 in the R&D proposal 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 these application guidelines.
- Current R&D PIs of the Advanced Research and Development Programs for Medical Innovation cannot be appointed as R&D PIs (with the exception of cases in which the R&D project term is to be reached by the end of FY2019).
- Multiple applications by the same research team whereby the R&D PI and R&D Co-Investigators interchange roles are not permitted under AMED-CREST.
- Making a current PRIME R&D PI an R&D Co-Investigator is not permitted under AMED-CREST (with the exception of cases in which the R&D project term is to be reached by the end of FY2019).
- If multiple selected proposals for 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 an R&D Co-Investigator for a proposal submitted to AMED-CREST and both proposals are shortlisted, adjustment 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.
- An applicant who is an R&D Co-Investigator under AMED-CREST can submit a proposal to PRIME. If the applicant is shortlisted as a candidate for PRIME, the applicant may need to reconsider their role as R&D Co-Investigator, or choose to withdraw the proposal for PRIME.
- Those who are submitting an application for LEAP for FY2019 may also submit an R&D proposal for AMED-CREST/PRIME in this round of solicitation. However, if the project for which the applications have been submitted becomes a candidate for selection for both AMED-CREST/PRIME and LEAP, the researcher in question shall be required to choose one of the R&D projects that they are conducting.

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

The restrictions on applicant eligibility due to conflicts of interest involving applicants and the Program Supervisor/Program Officer that were in effect through FY2017 are also not in effect with solicitations for this fiscal year.

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 research institute carrying out the R&D project and AMED.

*For details, please refer to Chapter V.

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

The Cross-ministerial Research and Development Management System (hereinafter referred to as "e-Rad"*) is a system that makes available online the series of processes relating to management of solicitation-based research funding systems at individual ministries and agencies (receipt of application => selection => management of selected projects => application to register research achievements and accounting reports). 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.

* "e-Rad" is the acronym for the Cross-ministerial Research and Development Management System, composed of the first letters of Research and Development, preceded by the "e" of electronic.

NB: e-Rad moved to a new system on Wednesday, February 28, 2018.
The screen design and menu structure have been totally refurbished form the perspective of improving usability. The manual for the new system has been uploaded to the e-Rad portal site, so please be sure to carefully check it.

(3) Registration with Japan Registry of Clinical Trials (jRCT)

Due to the promulgation of the Clinical Research Act (on April 1, 2018), registration with the Japan Registry of Clinical Trials (jRCT) database maintained by the Ministry of Health, Labour and Welfare and disease reporting, etc. are required when conducting clinical researches. Be sure to take the appropriate steps in compliance with the Act.

Clinical research initiated after the Clinical Research Act goes into effect should not be redundantly registered in the databases of Japanese clinical research registration institutions other than the jRCT. If the research has already been registered in the database of another clinical research registration institution in accordance with the "Ethical Guidelines for Medical and Health Research Involving Human Subjects," please take the appropriate action in accordance with laws and regulations, etc.

Please refer to Chapter IX. 15. for information on compliance with the Clinical Research Act.

(4) 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, guidelines, and directives, etc., issued by the Japanese government, beginning with the Foreign Exchange Act. In the case that R&D is carried out in infringement of relevant laws or guidelines, in

addition to the imposition of punishments and penalties according to legislation, the 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 Control"), 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 Control 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 Control technology to a foreign national (non-resident of Japan) or outside 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, DVD, 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
  http://www.meti.go.jp/policy/anpo/seminer/shiryo/handbook.pdf
- Center for Information on Security Trade Control
  http://www.cistec.or.jp/
  http://www.cistec.or.jp/english/index.html
- 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
  http://www.meti.go.jp/policy/anpo/law_document/tutatu/t07sonota/t07sonota_jishukanri03_eng.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 (Excluding indirect costs) *2	Period in which R&D is Scheduled to be Implemented	Planned Number of New Awarded Projects
1	Understanding of the biological phenomena and responses at the early life stages to improve the quality of health and medical care (PS: Hiroyuki Sasaki) (PO: Hiroyuki Takeda)	AMED-CREST*1	Max. of 300 million yen total period for each project	Max. of 5.5 years FY2019–FY2024	Around 3 ~ 6 projects
		PRIME	Max. of 40 million yen total period for each project	Max. of 3.5 years FY2019–FY2022	Around 8 ~ 12 projects
2	Understanding of pathophysiological processes and discovery of medical technology seeds through spatiotemporal research of tissue adaptation and repair mechanisms (PS: Akihiko Yoshimura) (PO: Takehiko Yokomizo)	AMED-CREST*1	Max. of 300 million yen total period for each project	Max. of 5.5 years FY2019–FY2024	Around 3 ~ 5 projects
		PRIME	Max. of 40 million yen total period for each project	Max. of 3.5 years FY2019–FY2022	Around 8 ~ 12 projects
3	Clarification of the mechanism of individual's functional impairment over the entire life course *3 (PS: Eisuke Nishida) (PO: Eiji Hara)	AMED-CREST	Max. of 300 million yen total period for each project	Max. of 5.5 years FY2019–FY2024	Around 2 ~ 4 projects
		PRIME	Max. of 40 million yen total period for each project	Max. of 3.5 years FY2019–FY2022	Around 8 ~ 12 projects

*1 When a proposal is submitted for unit-type (AMED-CREST) research in the R&D areas of "Understanding of the biological phenomena and responses at the early life stages to improve the quality of health and medical care" and "Understanding of pathophysiological processes and discovery of medical technology seeds through spatiotemporal research of tissue adaptation and repair mechanisms", AMED Reviewers affiliated with the overseas research institution will be added to the screening process, so the R&D proposal that is submitted should be partly in English.

*2 Indirect costs are 30% of R&D costs (direct costs).

*3 The 2019 solicitation will be the final call for submissions.

- "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.

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 Proposals" page on the AMED website.

https://www.amed.go.jp/en/news/proposals.html

(2) Period of Acceptance of Proposals

From Tuesday, April 9, 2019 to Tuesday, May 28, 2019 【Noon (JST)】(Observe strictly)

Note 1: Procedures for registering with e-Rad can only be carried out during e-Rad system operating hours.
Note 2: As the Application Deadline approaches, heavy demands on the e-Rad system could slow the application process and even result in the Application Deadline being missed. Please allow ample time for completing the proposal submission procedures.
Note 3: For all R&D proposals, applications received after the deadline will not be accepted
Note 4: After the period of acceptance of proposal documents has ended, AMED may contact the PI by e-mail or telephone, etc., to confirm administrative details. Please respond to such requests for confirmation promptly using the methods designated by AMED (if AMED does not receive a response, the proposal in question may be ineligible for review.)
Note 5: If not completed correctly, proposal documents may not be accepted.

(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 follow the guidelines provided in this item and on the R&D Proposal 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 (https://www.e-rad.go.jp/; https://www.e-rad.go.jp/en/). 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. Please appoint one person within the research institution to serve as a clerical affairs supervisor for e-Rad matters, and download the research institution registration application form from the e-Rad portal site and then fill out and submit it by postal mail. Registration 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 R&D programs or projects under the jurisdiction of other ministries or agencies. (If you have already registered with e-Rad for R&D programs or projects under the jurisdiction of other ministries or agencies, 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 not affiliated with a research institute shall be registered by e-Rad system operation managers at the Ministry of Education,

Culture, Sports, Science and Technology (MEXT). 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) File type

The data file for filled-out application forms, excluding those otherwise designated, can only be submitted in PDF format. e-Rad has a feature for converting Word and Ichitaro (Japanese document) files to PDF format. You may also download a PDF conversion software program and use it on your PC to convert the file. It is not necessary to use this feature or software for PDF conversion, but if you do use them, be sure to refer to user' manual (quick guide for researchers). 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.

2) Image file format

Image files for insertion in proposal documents should be submitted in "GIF", "BMP", 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 "Operation Manual (for reseachers)" section on the e-Rad portal site.

3) File capacity

The maximum size of single file that can be uploaded to the e-Rad system is 10 MB.

4) Uploading proposal documents

Please convert proposal documents to PDF format before uploading, excluding those otherwise designated.

5) "Temporarily save" input information

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

6) 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. Be sure to undergo procedures to obtain approval of the submission of the R&D project from your affiliated research institute.

7) Checking acceptance status

Verifying the acceptance of proposal documents can be done by viewing the "Manage submitted proposals" (応募課題情報管理) screen. After the researcher submits the application form, the application status will change to "Processing (Research Institution)" (研究機関承認待ち). Application documents whose application status has not changed to "Processing (Funding Agency)" (配分機関処理中) or "Accepted" (受理済) by the end of the acceptance period will become invalid. In the event that although a researcher has submitted the application documents prior to the end of the acceptance period and acknowledgment has been given by the clerical affairs supervisor their status remains unchanged as "Awaiting approval from research institution," please contact the section in charge.

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.

Do not "retrieve" R&D proposals on the day of the Application Deadline. On the day of the Application Deadline, there is a risk that the e-Rad system may be crowded and re-editing the proposal after retreiving it may take a very long time.

9) Other

Proposals containing incomplete or defective documents are excluded from the selection process. Read these "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.

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

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

Document review **July, 2019 (Tentative)**

Interview (hearing) **Listed below (Tentative)**.

R&D Area	AMED-CREST	PRIME
Understanding of the biological phenomena and responses at the early life stages to improve the quality of health and medical care	Aug. 7 (Wed)	Aug. 8 (Thu) Aug. 9 (Fri)
Understanding of pathophysiological processes and discovery of medical technology seeds through spatiotemporal research of tissue adaptation and repair mechanisms	Aug. 12 (Mon)	Aug. 13 (Tue) Aug. 14 (Wed)
Clarification of the mechanism of individual's functional impairment over the entire life course	Aug. 8 (Thu)	Aug. 9 (Fri) Aug. 10 (Sat)

Note 1: **In the case that a hearing is conducted, the PI for the relevant project shall as a general rule be contacted 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 will be contacted via e-mail and informed of hearing guidance, the date and time schedule of the hearing, and any additional documents to be submitted. In advance of the hearing, the PI may be asked to submit some documents such as proposal documents and R&D plans for other R&D funding programs. In cases where the R&D PI or Co-Investigators are affiliated with a profit-making organization, the PI may be asked to submit statements of accounts. 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 that interviews will in principle be conducted in Japanese, but that English may be used when conducting the interview in Japanese is impractical.

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. Applicants who are not selected in either the document-review or interview-based selection phase will be notified in writing and provided separately with an explanation of the reasons why the proposal was not selected.

Notification of Selection/Rejection **September, 2019 (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 Project (Contracting, Etc.) (Tentative date) **October 1, 2019 (Tue)**

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 between the time of the decision to adopt the project and the time the contracted 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,** as is the case with regard to the handling of all other items stipulated in these Application Guidelines. 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 Solicitation Briefing

A Solicitation Briefing **(NOTE: only in Japanese)** will be held as per the details shown below. The PS/PO will explain the operational outline and policy of each R&D area. Registration through the AMED website is required.

Date：April 25 (Thursday), 2019
Venue：FUKURACIA Tokyo Station "Meeting Room H"
Asahi-seimei Otemachi Bldg., 2-6-1 Otemachi, Chiyoda-ku, Tokyo, 100-0004
Registration Deadline：Apr. 23 (Tue), Noon, 2019 (through AMED website)

[Time Table]

Time	Contents
12:30 ~	Registration
13:00 ~ 13:40	Explanation of general rules of the program
13:40 ~ 14:20	Understanding of the biological phenomena and responses at the early life stages to improve the quality of health and medical care (Program Supervisor (PS): Hiroyuki Sasaki) (Program Officer (PO): Hiroyuki Takeda)
14:30 ~ 15:10	Understanding of pathophysiological processes and discovery of medical technology seeds through spatiotemporal research of tissue adaptation and repair mechanisms (Program Supervisor (PS): Akihiko Yoshimura) (Program Officer (PO): Takehiko Yokomizo)
15:10 ~ 15:50	Clarification of the mechanism of individual's functional impairment over the entire life course (Program Supervisor (PS): Eisuke Nishida) (Program Officer (PO): Eiji Hara)

Note 1: The explanation of general rules of the program is presented only once, from 13:00 to 13:40. Please note that the entire explanation will not be presented again during the explanations for each R&D area.
Note 2: Videos of explanations presented at the Solicitation Briefing may be viewed freely after the Briefing on the AMED website.

3. Method for Reviewing Proposal Documents

(1) Review Method

In accordance with AMED's "Regulations Regarding the Evaluation of R&D Projects", 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 shall evaluate specified items and then, based on the Panel's evaluations, AMED shall decide the R&D projects to be adopted. 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.

In addition, in order for AMED to contribute to the internationalization of the R&D environment as well as further enhance the quality of project evaluations, it has been decided to include researchers affiliated with an overseas research institution (AMED Reviewer) in the ex-ante evaluation process.*

* AMED Reviewers will participate in the ex-ante evaluation process for unit-type (AMED-CREST) projects in the R&D areas of "Understanding of the biological phenomena and responses at the early life stages to improve the quality of health and medical care" and "Understanding of pathophysiological processes and discovery of medical technology seeds through spatiotemporal research of tissue adaptation and repair mechanisms". When submitting project proposals in this area, please submit Appendix E2 "Security Trade Control Checklist" Please refer to Chapter II. 5. (4) for further information.

(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 conducting 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 a Mid-term Review and an Ex-Post Evaluation 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.

(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. (For details about publication on the AMED website, please refer also to Chapter IV.)

(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's "By-Law Regarding the Treatment of Conflict of Interest Management for Members of the Research & Development (R&D) Project Review Panel". 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, Program Director (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.

Document reviews will place particular emphasis on the perspectives stated in (a), (b), and (c), but when necessary the perspectives stated in (d), (e), and (f) will also be taken into consideration. In the interview screening (hearing), evaluations and reviews will be conducted based on all six perspectives.

(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 achievements of the aims of the R&D? In addition, is 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?
- Are the plans for each fiscal year detailed and realizable?
  (Have milestones been 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 the collaboration framework been constructed sufficiently to enable the R&D Co-Investigator to significantly contribute to the achievement of R&D initiatives?)
- In the case of PRIME, is the proposed R&D project of an appropriate scale for individual researchers to be able to carry out the project?

- 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 to realize 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 Chapter 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 rights and interests of the applicant are in no way unfairly infringed. 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 related to each adopted project (program title, R&D project title, PI's affiliated institution/position/name, e-Rad project/researcher/research institution number, budget amount, R&D period, outline/abstract or Contracted R&D Accomplishments Report (public information))[1] may be sorted, classified, and made public on AMED's website, the AMED R&D projects database (AMEDfind), and public databases operated by funding agencies, etc., providing cooperation under an agreement, etc., with AMED (World RePORT,[2] etc.). In addition, with regard to all projects for which applications have been submitted, information requiring micro-analysis will be analyzed by AMED and the analysis results provided to related government ministries and agencies as well as funding agencies, etc., and made public, and may also be posted on funding information databases, etc.[3] For this reason, even after the relevant project has been selected, researchers are requested to input into e-Rad the R&D accomplishment information for each fiscal year (academic papers, patents, etc.) as well as accounting report information and information on actual disbursement of indirect costs related to competitive funding.

[1] Information shall be treated as "information expected to be made public" as per the stipulations of Article 5, Item (i) (a) of the Act on Access to Information Held by Independent Administrative Agencies (Act No. 140 of 2001). Furthermore, the same shall apply to the above-mentioned items shown on the Contracted Items Sheet that is to be completed if the relevant project is adopted.

[2] What is "World RePORT"?

"World RePORT" is a database for international collaborative research supported by research funding agencies in major countries. Its purpose is the visualization of international research collaboration carried out by various countries, which was previously difficult to verify. Managed and operated by the United States' National Institutes of Health (NIH), the database currently records information for twelve research funding agencies around the world, including the NIH, the UK's Medical Research Council (MRC), the Bill & Melinda Gates Foundation (BMGF), European Commission (EC), Canadian Institutes of Health Research (CIHR), and the Wellcome Trust. https://worldreport.nih.gov/app/#!/about

[3] "Databases, etc." includes World RePORT, ERP and other databases.

(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

The following forms are required for the application. Please note that the forms that must be submitted and the language that should be used will differ depending on the R&D area and the type of research (AMED-CREST or PRIME). Be sure to fill out each item in the documents concisely and clearly. With regard to the acceptance period for proposal documents and submissions, please refer to Chapter III.

R&D areas of "Understanding of the biological phenomena and responses at the early life stages to improve the quality of health and medical care" and "Understanding of pathophysiological processes and discovery of medical technology seeds through spatiotemporal research of tissue adaptation and repair mechanisms" (AMED-CREST)

Format	Contents	Language
Form E1	R&D Proposal Cover Page (in Engish), 1. Research Objectives, 2. R&D Plan and Approaches, 3. Research Achievements, Annex E1 Main Schedule for R&D	English*1
Form E2	R&D Proposal Cover Page (in Japanese), 4. Status of Research Application, Acceptance, and Effort, 5. Past Research Funds/Grants Received and Resulting Achievements Annex E2 Implementation System Diagram, Annex E3 R&D Project Organization (R&D PI's Group and Co-Investigator's Group), Annex E4 Ethical Considerations, Annex E5 References and Additional Statements	Japanese
Appendix E1	Summary or Proposal (in Japanese)	Japanese
Appendix E2	Security Trade Control Checklist (in Japanese) Summary of Proposal (in Engish)	Japanese English
Appendix E3	List of R&D PIs and Co-Investigators (to submit as an Excel format)	Engish

*1 When the application is being submitted for the unit-type (AMED-CREST) projects in this R&D areas, AMED Reviewers affiliated with overseas research institutions will participate in the review process. For this reason, you should fill out and submit Form E1 in English, and also submit Appendix E2 "Security Trade Control Checklist" and Appendix E3 "List of R&D PIs and Co-Investigators (to submit as an Excel format)."

*2 **Please be assured that the content of Appendix E2 "Security Trade Control Checklist" will not affect the evaluation.**

R&D area of "Clarification of the mechanisms of individual's functional impairment over the entire life course" (AMED-CREST)

Format	Contents	Language
Form J1	R&D Proposal Cover Page, 1. Research Objectives, 2. R&D Plan and Approaches, 3. Research Achievement, 4. Status of Research Application, Acceptance, and Effort, 5. Past Research Funds/Grants Received and Resulting Achievements, Annex J1 Main Schedule for R&D, Annex J2 Implementation System Diagram, Annex J3 R&D Project Organization (R&D PI's Group and Co-Investigator's Group), Annex J4 Ethical Considerations, Annex J5 References and Additional Statements	Japanese
Appendix J1	Summary of Proposal (in Japanese)	Japanese
Appendix J2	Summary of Proposal (in English)	English

All R&D Areas for PRIME

Format	Contents	Language
Form P1	R&D Proposal Cover Page, 1. Research Objective, 2. R&D Plan and Approaches, 3. Research Achievement, 4. Status of research application, acceptance and effort, 5. Past research funds/grants received and resulting achievements Annex P1 Main Schedule for R&D, Annex P2 Research Organization, Annex P3 Ethical Considerations, Annex P4 References and Additional Statements	Japanese
Appendix P1	Summary of Proposal (in Japanese)	Japanese
Appendix P2	Summary of Proposal (in English)	English

(2) Preparation of Proposal Documents

Applications are to be submitted via e-Rad. Please download the proposal document forms from the e-Rad portal website or the AMED website which are provided in Chapter III. 2 and Chapter X. 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.

For details regarding the evaluation, please refer to Chapter III. 3. For details regarding security trade control, please refer to Chapter II. 5. (4).

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

(a) For forms in the R&D Proposal for which language is specified as shown in the table above, fill out the form in the specified language. 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. Forms for which language is specified as “Japanese” can be filled out in English if you have difficulty writing in Japanese.

(b) With regard to formats prescribing word limits or page limits, please be sure to comply with the set limits. Fill out the forms as concisely and clearly as possible, even when there are no limitations on the number of pages.

(c) With regard to letter/character size when inputting information, please use 10.5 point as a general rule, with the paper size of A4 for all forms.

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

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

(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 Proposals

(a) Compliance with laws and 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 affiliated institutions

In submitting proposal documents, the PI must obtain the approval of the Principal Institution (research institute with which the PI is affiliated and which is to conclude a direct contracted agreement with AMED). For all participating Subsidiary Institutions also, obtain the approval of the institution and then note in the R&D Proposal that approval has been obtained. (Change the □ in the proposal to ■).

(c) Revision of 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 facilities and 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 science 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 science 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. 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 study, etc.

For research undertaking investigator-initiated trials or clinical studies with a view to creating innovative drugs or medical devices, or nonclinical studies aimed at conducting such trials/studies,* applicants are required to submit materials related to the clinical study 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 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 may be 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.

(d) Documents etc. regarding management of R&D

From the perspective of verifying the appropriateness of R&D management, from now on there may be requests to submit the indicated documents relating to pharmaceuticals. In addition, where necessary inquiries regarding content may be made.

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 research institution implementing the R&D project* and 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. Subsidiary Institutions must conclude a subcontracted R&D agreement with the Principle Institution for implementing the R&D project.

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 plan may be revised or suspended (including early conclusion of projects due to achievement of R&D plans).

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.

  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 government inspection and auditing by AMED in response to requests from AMED.

(2) Preparations for Concluding Agreement

Following the adoption of an R&D project, the research institution implementing the R&D project 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 a Mid-term Review and an Ex-Post Evaluation, 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: https://www.amed.go.jp/keiri/index.html

(4) Ensuring the Research Period through the End of the Fiscal Year

To enable R&D to be conducted through the end of the fiscal year, the Contracted R&D Accomplishments Report should be submitted to AMED no later than the 61st day (the last day of the month after next) as calculated

from the last day the Contracted R&D execution period. Each research institute should work to put in place the necessary mechanism in-house to ensure a research period up through the end of the fiscal year is secured.

(5) 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. 8. (2)).

2. Scope and Payment of Contracted R&D Funds

(1) Scope of Contracted R&D Funds

In accordance with the governmental ministries' and agencies' expenditure table used in common for the competitive funds, items of expenditure have been set as follows for the program. For details, please refer to the AMED's "Administration Manual for Contracted R&D Agreement."[1]

	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/ services costs	Personnel costs: personnel costs for researchers, etc., employed to conduct the relevant contracted R&D[2] Service costs: expenditure for services such as lecture requests, guidance/advice, test subjects, interpretation/translation, 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, licensing fee, amount equivalent to consumption tax related to untaxed transactions, etc.
Indirect costs[3]	Expenditure used by research institutes as necessary costs for managing the research institutes during implementation of the relevant R&D, paid at a fixed percentage of direct costs (with a 30% rule of thumb) as an allowance.	

[1]Link from: https://www.amed.go.jp/keiri/index.html

[2]As a rule, under this program personnel costs for the R&D PI or Co-Investigator cannot be disbursed from direct costs. However, in the case of PRIME, please inquire individually in cases such as when, under the employment conditions of your affiliated research institution, your personnel costs are paid from external funds that you have been 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). The fixed percentage will not exceed 30%. 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."*

Please note that payment by note, netting, and factoring are not accepted.

* Link from: https://www.amed.go.jp/keiri/index.html

Note: Contracted R&D agreements for researcher-initiated trials or clinical studies under AMED shall employ "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 Studies" (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 Studies" (link from: https://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) Diversion of costs between items

When the diverted amount for each cost item (main item) does not exceed fifty percent (50%) of direct costs (or five million yen (JPY 5,000,000), if the amount equal to fifty percent (50%) of direct costs is less than five million yen (JPY 5,000,000)) for that fiscal year, the amount may be diverted without approval from AMED on the assumption that the diversion is appropriate and consistent with the R&D plan. For details, please refer to the AMED "Administration Manual for Contracted R&D Agreement."*

* Link from: https://www.amed.go.jp/keiri/index.html

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

You should prepare documentary evidence of appropriate expenditure, from the standpoint of ensuring transparency of use as noted in the "Common guidelines relating to the expenditure of indirect costs for competitive fund" (revised on May 29, 2014 at the liaison meeting of relevant Ministries on competitive fund) and retain it for a period of five years following the year of the completion of the R&D project. A Report on Indirect Cost Expenditures must be prepared for the expenditure of indirect costs for each fiscal year and submitted by June 30 of the following year. For details, please refer to the AMED "Administration Manual for Contracted R&D Agreement."*

* Link from: https://www.amed.go.jp/keiri/index.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: https://www.amed.go.jp/keiri/index.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. 6. and the AMED website.)

Furthermore, in the case that a researcher does not fulfill their obligation to undergo the 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" and Article 21 of the Ordinance for Enforcement of the Clinical Research Act, 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 Chapter V. 7. and 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 guidelines that must be complied with, in addition to the imposition of punishments and penalties according to legislation, 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 the guarantee 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 an item shown in the Contracted R&D Accomplishments Report.

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)
- Clinical Research Act (Act No. 16 of 2017)
- 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)
- Ordinance for Enforcement of the Clinical Research Act (Ordinance of the Ministry of Health, Labour and Welfare (MHLW) No. 17 of 2018)
- 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. 1 of 2017)
- 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)

- Guidelines on Opportunities for Acquisition of Genetic Resources and on Fair and Equitable Distribution of the Profits Generated through their Use (Public Notice of the Ministry of Finance (MOF), the Ministry of Education, Culture, Sports, Science and Technology (MEXT), the Ministry of Health, Labour and Welfare (MHLW), the Ministry of Agriculture, Forestry and Fisheries (MAFF), the Ministry of Economy, Trade and Industry (METI), and the Ministry of Environment (MOE) No. 1 of 2017)

* 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 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," and research funds shall be managed under the responsibility of research institutes.

(6) Response Obligations Regarding System Maintenance, etc.

(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 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)

* Please refer to the following websites for details of each guideline.
・Guidelines for Responding to Misconduct in Research Activities
http://www.mext.go.jp/b_menu/houdou/26/08/1351568.htm
・Guidelines for Management and Audit of Public Research Funds at Research Institutions (implementation standards)
http://www.mext.go.jp/a_menu/kansa/houkoku/1343904.htm

(b) Confirmation of system maintenance

In concluding the agreement for the program, each research institution will be asked to submit to the following checklist to MEXT regarding the implementation status of system maintenance based on the various guidelines.

According to the format of the various websites all research institutes are requested to submit a checklist to MEXT via e-Rad by the deadline stipulated seperatey by AMED.

1) Self-evaluation (Including System Maintenance) Checklist
   - Basis: Guidelines for Management and Audit of Public Research Funds at Research Institutions (implementation standards)
   - Submission method: http://www.mext.go.jp/a_menu/kansa/houkoku/1301688.htm
   - Submit to: Office of Research Funding Administration, Promotion Policy Division, Research Promotion Bureau, MEXT
2) Checklist of research misconduct
   - Basis: Guidelines for Responding to Misconduct in Research Activities
   - Submission method: http://www.mext.go.jp/a_menu/jinzai/fusei/1374697.htm
   - Submit to: Office for Research Integrity Promotion, Knowledge Infrastructure Policy Division, Science and Technology Policy Bureau, MEXT

(c) Necessity of submitting a checklist

With regards to the checklists 1) and 2) cited above in (b), in the case that applicants 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 MEXT program or concluding a contracted R&D agreement in the same fiscal year.

Furthermore, for the Checklist of 2), it is not necessary for a checklist to be newly submitted by institutions that are not conducting research or by institutions that are conducting research but is an institution to which the budget is not allocated or provided by MEXT or an independent administrative agency under MEXT's jurisdiction.

However, both of these checklists are required to be submitted on an annual basis, so research institutes that are continuing implementation in the following year and beyond must also submit the checklists to 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 “How to Register (for reserachers)” section on the following websites provided for research institutes affiliated with e-Rad.

https://www.e-rad.go.jp/organ/index.html

(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 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 system improvement that a research institute’s system improvement is inadequate shall be issued management conditions by MEXT stating the items requiring improvement and the deadline for implementing these improvements. In addition, in cases in which the management conditions are not deemed to have been fulfilled by the research institute it may become subject to measures such as reducing the indirect costs with regard to all competitive funding allocated by MEXT and independent administrative agencies under the jurisdiction of MEXT.

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

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

Researchers participating in 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 participate in this program 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 refer to Chapter V. 6. for details.) 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.

6. Participation in Research Ethics Program

(1) Persons Required to Undergo Ethics Training/Program(s) to be Undertaken/Educational Materials

Research institutions, etc., should ensure that researchers who are deemed to be substantially participating in research activities that are being conducted using research funding provided by AMED undergo training using one of following programs/materials.

・APRIN e-Learning Program (eAPRIN)

・“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

Furthermore, the Clinical Research Act stipulates that the “Kenkyusekinin Ishi” (Principal Investigator) and “Buntankenkyu Ishi” (Co-Investigator) must undergo sufficient education and training regarding research-related ethics and the knowledge and skills of the research methods required for implementation of the research in order to carry out the relevant clinical research appropriately in accordance with their required responsibilities. Researchers required to undergo training must undertake one of the following training programs.

(a) Training conducted by a Clinical Research Core Hospital for persons working in the clinical research field.

(b) Training that is recognized by the research institution as being equivalent to the above (including training conducted by facilities other than a Clinical Research Core Hospital)

Note 1: Simply participating in academic meetings does not qualify as education/training.
Note 2: Certain quality-assured e-learning programs such as APRIN e-learning program (eAPRIN), Clinical Research e-Training Center (Center for Clinical Trials, Japan Medical Association), Introduction to Clinical Research (ICRweb) may also be acceptable for (b), but it is essential that the Principal Research Physician undergoes thorough training and understands the training content.

(2) 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.)

(3) Role of Research Institutes

Research institutes shall ensure that persons required to undergo research ethics training as listed in (1) above who are affiliated with their institution (included a subcontracted institution) 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.

(4) 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 FY2019
Deadline for submission: May 31, 2020
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: https://www.amed.go.jp/kenkyu_kousei/kyoiku_program.html
Information regarding where and how to submit reports is to be posted on the “The Responsible Conduct of Research (RCR) Education Program” page under “Research Integrity” on the AMED website (refer to URL shown above) around March 2019.

(5) 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.)

7. COI Management

(1) Conflict of Interest Management in Accordance with AMED’s “Regulations Regarding Conflict of Interest (COI) Management in Research Activities”

1) Target persons
PI or Co-Investigator of R&D projects
Projects on the List of Non-R&D Projects on the AMED websites Research Integrity page’s “COI Management in R&D” are excluded as targets.

2) 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.

(2) Conflict of Interest Management in Accordance with Article 21 of the Ordinance for Enforcement of the Clinical Research ACT

Please carry out conflict of interest management in accordance with relevant laws and ordinances.

(3) Submission of Reports on the State of COI Management

Each research institution, etc. with which the R&D PI and Co-Investigators are affiliated should prepare a Report on the State of COI Management for each project, and submit it to the Department of Research Integrity and Legal Affairs in electronic file form. (The research institute should also compile and submit a report by the Co-Investigator at subcontracted 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.

Information regarding where and how to submit reports is to be posted on the "Conflict of Interest (COI) Management in R&D" page under "Research Integrity" on the AMED website (refer to URL shown above) around March 2019.

https://www.amed.go.jp/kenkyu_kousei/riekisohan_kanri.html

(4) 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
- Regulations Q&A
- Reports on the State of COI Management

https://www.amed.go.jp/kenkyu_kousei/riekisohan_kanri.html

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

(1) Reporting of and Cooperation in Investigations of Misconduct, Fraudulent Use, and Fraudulent Receipt

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 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); and AMED Regulations for Responding to Misconduct in Research Activities.

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.

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 (decided by the Minister of Education, Culture, Sports, Science and Technology on August 26, 2014); Guidelines for Management and Auditing of Public Research Costs in Research Institutions (implementation standards)" (decided by the Minister of Education, Culture, Sports, Science and Technology on February 15, 2007; revised on February 18, 2014); and AMED Regulations for Responding to Misconduct in Research Activities.

(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 the Guidelines for Responding to Misconduct in Research (decided by the Minister of Education, Culture, Sports, Science and Technology on August 26, 2014) ; Guidelines for Management and Auditing of Public Research Costs in Research Institutions (implementation standards)" (decided by the Minister of Education, Culture, Sports, Science and Technology on February 15, 2007; revised on February 18, 2014); and AMED Regulations for Responding to Misconduct in Research Activities.

(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. In the event that contracted R&D funds are returned, the relevant research institute will be required to pay interest calculated in accordance with the number of days from the date of the receipt of contracted R&D funds until the date of return. The interest will be determined by AMED within the scope of 10.95% per annum for the contracted R&D funds (if a portion of the amount has been returned already, the already returned amount will be subtracted from the balance for the remaining time). 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 to and eligibility for 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 eligibility for participation in AMED programs restricted in accordance with the degree of misconduct as shown in the table below.

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 eligibility for participation in AMED programs, the researcher's application to and eligibility for 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.

[In the case of misconduct]

The period of restriction deemed appropriate in consideration of the misconduct and its nature, on or after the day that the misconduct is recognized, and between one year and ten years from the fiscal year in which the day on which the misconduct is recognized or the next fiscal year.

Category of misconduct according to involvement		Degree of misconduct	Period deemed appropriate
Person Involved in the	1. Especially malicious individual who intentionally engages in misconduct from the outset of the research		10 years

<table>
<tr><td rowspan="4">Misconduct</td><td rowspan="3">2. Author of academic paper, etc. related to research in which there has been misconduct</td><td>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></td><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 etc. of the fraudulent use/fraudulent receipt, on or after the day that AMED decides upon the measures, and between one year and ten years from the fiscal year in which the day on which AMED decides upon the measures 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 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

Note 1: In the following cases, the offender shall be given a reprimand without imposing restrictions on eligibility for participation.

- 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, the person's actions are deemed to have a small social impact and be slightly pernicious.

Note 2: With regard to 6 above, periods will be decided upon with due consideration of the extent of violation by the researchers with duty of diligence.

(c) Restrictions on researchers whose application to and eligibility for 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 eligibility for participation in these programs has been restricted, application to and eligibility for 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 (a) and (b) above are implemented under this program, the content of the relevant measures shall as a general rule be publicly disclosed in accordance with the Guidelines for Responding to Misconduct in Research (decided by the Minister of Education, Culture, Sports, Science and Technology on August 26, 2014) ; Guidelines for Management and Auditing of Public Research Costs in Research Institutions (implementation standards)" (decided by the Minister of Education, Culture, Sports, Science and Technology on February 15, 2007; revised on February 18, 2014); and AMED Regulations for Responding to Misconduct in Research Activities. In addition, the misconduct may be disclosed by the related government ministries/agencies.

Furthermore, as both MEXT guidelines state that when misconduct is identified the research institute must swiftly publicize the results of its findings all institutes are asked to take the appropriate steps. MEXT currently makes public an outline of matters of misconduct, so please refer to these at the following web pages.*

* http://www.mext.go.jp/a_menu/jinzai/fusei/1360483.htm
http://www.mext.go.jp/a_menu/kansa/houkoku/1364929.htm

(3) Registration with AMED RIO Network

To promote research integrity activities in an efficient manner, it is essential for AMED and the research institution or research institutions among themselves to exchange information and work together. Accordingly, to promote efficient research integrity activities nationwide, the RIO Network was established in FY2017 to provide a venue where the Research Integrity Officers (RIO) of research institutions which are allocated research funds from AMED can easily exchange information. Detailed information on the RIO Network is provided on the following website:

* https://www.amed.go.jp/kenkyu_kousei/rionetwork.html

The officers in charge of R&D ethics education and the officers in charge of promoting compliance (collectively referred to as "Research Integrity Officers" or RIO) who are participating in AMED programs should become members of the RIO Network.

There is a space on the "Breakdown of Expenses, etc. and Contracted Items Sheet," which is submitted when the contract is concluded, for entering information about the officers in charge of R&D ethics education and the officers in charge of promoting compliance, so be sure to fill in this information. AMED will register Research Integrity Officers with the RIO Network. When registering personnel other than the above who are engaged in

research integrity related tasks with the RIO Network, please do so in accordance with the instructions on the AMED RIO Network website.

9. 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 project have had their application to/eligibility for participation in AMED R&D programs restricted for a certain period of time.
- An investigation has been opened into allegations of misconduct.
- Conditions that were set for adoption of the R&D project ultimately have not been fulfilled.
- It is discovered that the R&D project does not fulfill the conditions for solicitation, etc.

(2) Representation and Warranty for Researchers Undergoing Investigation/Researchers Discovered to Have Undertaken Misconduct

Please note that in concluding contracted R&D agreements, AMED requires Principal Institutions 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 under this program), 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* or AMED Regulations for Responding to Misconduct in Research Activities, but excluding, however, persons regarding whom restrictions have not been placed regarding application to/eligibility for 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/eligibility for 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 or AMED Regulations for Responding to Misconduct in Research Activities are affiliated with the research institute in question and either the R&D PI or Co-Investigator (if there is a subcontracted institute, including the Co-Investigator or equivalent person affiliated with the subcontracted institute) for the R&D Plan, AMED has been notified of the relevant target persons by the day before the contracted R&D agreement will be 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 institute (from AMED's perspective, a subcontracted agreement. Hereinafter, the third party institute shall be referred to as the "subcontracted institute"), 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).

Note: The "Japanese Government guidelines for responding to misconduct" referred to in this section is a blanket term for all of the various policies and guidelines concerning response to misconduct formulated by the Japanese Government.

(3) Submission of R&D Plans and Reports

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

(4) Submission of Data Management Plans

With regard to awarded projects, the PI is requested to submit a data management plan* to AMED when they conclude a contracted R&D agreement after adoption.

* With regard to R&D projects conducted using public funds in which there is a need to sort and systemize (make databases) of data, the submission of a data management plan helps to strengthen management and catalytic functions by enabling AMED to ascertain the location of research data, and is useful in the joint promotion of different R&D projects to the furthest extent possible, and also helps to avoid duplicative research.
It is requested that data management plans include the program year, program name and R&D project name, a general term for the data and data sets deriving from the project, an explanation of the R&D data, the affiliation and name of the data scientist and repository and any other requisite details. A separate form will be sent to successful applicants in due course.
The name and affiliation of the data scientist may be published along with other project details unless the data scientist wishes to remain anonymous.
It is planned to upload the details on the AMED website.

(5) 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 multiple competitive research funding programs 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 on an overlapping basis.
- 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
- There 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 researchers’ time exclusively spent for the R&D activities concerned against the researcher’s annual working hours. Researchers’ total working hours refer to not only the time spent in research activities but also total substantive working hours, including educational/clinical 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 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 and/or 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 and/or 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 the 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 similar coordinative actions.

  Note: 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 thoroughly 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). Please note that, depending on the progress status, review of the project plan or cancelation (early conclusion) of the project may be carried out.

For research undertaking investigator-initiated trials or clinical studies with a view to creating innovative drugs or medical devices, or nonclinical studies aimed at conducting such trials/studies* during the R&D period, research institutes are required to submit materials related to clinical studies 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).

* Does not include clinical research that is not aimed at developing 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 a Mid-term Review by the “Project Evaluation Panel” at around 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. *1*2 Awarded projects whose planned project period is less than five years are not required to undergo a Mid-term Review as a general rule, but in the case that it becomes necessary to conduct a Mid-term Review in the course of implementing the program, a Mid-term Review 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 a Mid-term Review, regardless of the timing. Based on evaluation results, AMED may cancel (conclude early) in accordance with the overall decision of the PS and PO, etc.

In addition, all awarded projects are to undergo Ex-Post Evaluations at an appropriate time following the conclusion of the R&D project. Moreover, a follow-up evaluation may be carried out after a certain period of time after conclusion of the project if deemed necessary.

*1 In the case of PRIME research, a Mid-term Review will not be conducted unless one is determined to be necessary.
*2 “Five years” refers to five fiscal years.

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 evaluations 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 R&D accomplishment reportings, intellectual property (IP) and usage of R&D accomplishments.

1. Submission and Publication of R&D Accomplishments Reports

Contractors shall submit a 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 R&D accomplishments report is not submitted by the deadline, it shall be deemed that the contracted R&D agreement has not been fulfilled, so please be sure to strictly comply with the submission deadline.

A part of the items in the R&D accomplishment reports and outline of accomplishments will be treated as publicly open information. As it will be published at appropriate times on the AMED website please be careful to indicate parts that are not to be made public in the section “Non-Disclosure Items” in the reporting form with regard to information about patents that are pending but have not been published in an official gazette, knowhow and other confidential sales information and any other undisclosed information. Moreover, with regard to final accomplishment reports produced at the end of research projects that have lasted for several years, the content under the section of “Items for Disclosure” in the reporting form compiled by the PI upon Ex-Post Evaluation will be published at appropriate times on the AMED website.

2. Attribution of R&D Accomplishments

With regard to patent rights, copyrights and other intellectual property (IP) relating to R&D accomplishments, these can revert to the contractor under the condition that the requirements provided for in Article 19 of the Industrial Technology Enhancement Act (Act No.44 of 2000, the Bayh-Dole Act. The Japanese version of the Bayh-Dole Act) are satisfied. The purpose 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 efficiently 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 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.

3. Measures towards the Practical Application of R&D Accomplishments

Contractors are requested to maintain a strong sense of awareness that they are in a position in which they must try their best to use the accomplishments of the R&D entrusted to them by AMED in order to make a contribution to society, implement them and put them to practical use, and take the requisite measures towards this goal. In particular, they are requested to make the maximum use of inventions, knowhow, data and other IP, while in accordance with AMED's IP policy* ensuring that appropriate measures have been implemented within the contractor’s funding sources such as appropriating indirect costs, and costs for obtaining IP rights in order to ensure appropriate protection and utilization of patent rights and other IP rights on a global scale.

AMED’s Department of Intellectual Property provides consistent support for maximizing and achieving the practical application of R&D accomplishments that have reverted to the contractors, so do not hesitate to contact the Medical IP Desk (For details, please refer to Chapter IX. 7.).

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

4. IP Educational Materials for Medical Researchers

IP educational materials for medical researchers are 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.

In addition, AMED has prepared e-learning IP educational materials for researchers selected for the AMED program with the objective of deepening understanding of strategies for the IP applications peculiar to the field of medicine, utilization strategy and Bayh-Dole reports obligated according to agreements. It is a requisite that these IP educational materials are studied by researchers in the case of some programs. Details will be provided later about how to access these e-learning IP educational materials

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

5. 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 university corporations, 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 than “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 Companies etc., may continue to borrow free-of-charge tangible property and whose ownership has reverted to AMED for the duration of its service life and the tangible property may be transferred to the Companies etc., for a fee upon the evaluation of AMED 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

While these items do not impact evaluations under each program unless noted as a special condition, AMED requires grant program participants to proactively endeavor to adhere to comply with each of these items due to their importance. Research institutions and researchers are asked to gain a thorough understanding of the purposes of these items and comply with these in carrying out their R&D. Moreover, to ensure that the results of these efforts contribute to the improved implementation of AMED programs in the future, not only may they be used in analysis of research trends, but also the analysis results may be publicized in a form that does not identify the R&D project (E.g.: published by program rather than individual project). Accordingly, it is required that this information is included in Contracted R&D Accomplishments Reports.

1. Promotion of Dialogue and Cooperation with Citizens and Society

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. The 5th Science and Technology Basic Plan (decided by a Cabinet Decision on January 22, 2016) demands that science and technology and society, which have traditionally worked at cross purposes, need to have a deeper relationship in order to facilitate dialogue and cooperation, or “co-creation,” between a diverse range of stakeholders, including researchers, citizens, media, industry, and policymakers. From this perspective, there is a need for initiatives to explain research activity contents and their results and accomplishments in a comprehensible manner to society and the general public, and to promote dialogue and cooperation with many stakeholders. In response to this, research institutions are requested to hold public meetings and symposia, about their R&D accomplishments and continuously post their R&D accomplishments on the Internet, and eagerly involve themselves in round table meetings etc. that include the participation of a wide spectrum of stakeholders.

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

2. Promotion of the Patient and Public Involvement (PPI) in Medical Research/Clinical Studies[1]

AMED’s mission is to approach each patient individually, staying close and providing support for LIFE (being alive, living each day, living life) while ensuring the practical application of research results in the medical field as quickly as possible and delivering these results to patients and their families. In view of this mission, AMED is promoting initiatives that promote Patient and Public Involvement (PPI) in medical research and clinical studies. These efforts are expected to generate research results that are even more beneficial to patients, etc., as well as lead to smoother implementation of research and improved protection of clinical trial subjects. For these reasons, AMED requests that program participants proactively incorporate PPI into medical research and clinical studies. Moreover, for the time being it is envisages that among the areas of medical research and clinical studies the PPI initiative will mainly focus on investigator-initiated trials, intervention studies, observational studies (non-intervention studies) with human subjects.

[1] AMED’s definition of “Patient and Public Involvement (PPI) in Medical Research/Clinical Studies”
As part of the medical research/clinical study process, researchers are endeavoring to incorporate the knowledge and opinions of patients and members of the general public. Here, “Patient and Public” includes patients, patients’ families, former patients (survivors), and future patients.
(Reference) AMED’s “Patient/Public Involvement (PPI) in Medical Research/Clinical Studies”
https://www.amed.go.jp/ppi/index.html

3. 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[1]. 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 https://www.amed.go.jp/keiri/index.html

4. Registration of Researcher Information on Researchmap

Researchmap* is the largest database in Japan serving as a list of researchers in the nation. It enables researchers to publicize their registered accomplishments over the Internet. In addition, researchmap links in with e-Rad and many university databases of researchers, and since the information registered on it can be used on other systems it makes it unnecessary for researchers to repeatedly input information in multiple application forms about accomplishments and applications on various databases. The information registered on researchmap is effectively used in governmental and other science and technology policy making research and for statistical purposes, and those carrying out projects under this program are therefore requested to cooperate by registering with researchmap.

* http://researchmap.jp/

5. 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.

6. 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 under this program carries 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
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

7. IP Consultation Support through AMED IP Consultants and AMED IP Liaisons

In order to encourage the practical application of R&D accomplishments obtained from AMED projects implemented, AMED provides a free-of-charge IP consultation service run by AMED IP Consultants covering IP strategy and licensing strategies. Furthermore, as one facet of this IP consultation service, when requested we also provide a free service to formulate precise IP strategies for R&D accomplishments through investigating the available literature, etc.

In addition, the AMED IP Liaison visits research institutions throughout the nation and in conjunction with the AMED IP Consultants help to create a system enabling consultation at an early stage regarding appropriate out-licensing of R&D accomplishments obtained. Specifically, the AMED Liaison[1] provides 1) IP strategy advice aimed at appropriate out-licensing at the early stages of R&D, 2) investigations of the available literature, markets research and support for technical seeds evaluation, and 3) guidance for the creation of appropriate PR sheets on R&D accomplishments for exhibitions and business negotiations.

If you wish to receive the support mentioned above, please contact AMED's Medical IP Desk. Please refer to the website[2] below for information regarding the Medical IP Desk.

[1] AMED IP Liaisons: https://www.amed.go.jp/chitekizaisan/chizai_riezon.html

[2] Medical IP Desk: https://www.amed.go.jp/chitekizaisan/medical_ip_desk.html

8. Seeds/Needs Matching Support System

In April 2018, AMED launched the "AMED PLAT" private information network system, the purpose of which is to match at the earliest possible stage the R&D seeds information of universities and other academia with corporate needs information, providing support aimed at achieving early practical application and commercialization of R&D results in the medical field. This enables outstanding research seeds to be showcased to staff in charge of in-licensing at multiple companies, facilitating university-company collaboration at an early stage. To this end, detailed information about how to proactively register research seeds in the medical field in the AMED PLAT system and begin using the system is provided on the AMED PLAT website.

Please use the AMED PLAT website: https://www.amed.go.jp/chitekizaisan/amed_plat.html.

9. 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 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.

In the same way, with regards to the applied R&D projects related to drug development that is or was supported by the Drug Development Department, AMED provides the information on the support content to the department in charge of the program.

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

10. 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.

11. Cooperation with Databases

(1) Public Disclosure of Data from the National Bioscience Database Center (NBDC)

The National Bioscience Database Center (NBDC) (https://biosciencedbc.jp/) was established by the Japan Science and Technology Agency (JST) in April 2011 with the objective of promoting comprehensive usage of databases in the life science field that have been created by various research institutions. Under the report "Progress and Future Direction of the Life Science Database Integration Coordination Program" (January 17, 2013), the NBDC is to take a central role in expanding the scope of projects eligible to be granted access to data and/or databases.

Accordingly, we request your cooperation with regard to NBDC's public disclosure of the following types of data and/or databases obtained through projects conducted under AMED-CREST/PRIME.

No.	Type of data	Place of public disclosure	URL of place of public disclosure
1	Overview of databases for public disclosure that have been constructed	Integbio Database Catalog	https://integbio.jp/dbcatalog/
2	Copies of data for published research results, such as academic paper presentations, or copies of databases for public disclosure that have been constructed	Life Science Database Archive	https://dbarchive.biosciencedbc.jp/
3	Of the data/databases of 2, those that are related to humans	NBDC Human Database	https://humandbs.biosciencedbc.jp/

(2) Use of the National Bioresource Project (NBRP) Resource and Deposit of Developed Resources to NBRP

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[3] the relevant bioresources to institutions participating in the NBRP[1] Core Facility Upgrading Program[2] (limited to bioresources targeted by the NBRP), making these resources broadly available for researchers' use. Use of bioresources that have already been prepared at NBRP is recommended from the standpoint of efficient project execution, etc.

[1] NBRP: https://www.amed.go.jp/program/list/04/01/002.html
[2] NBRP Core Facility Upgrading Program: NBRP Information Site
http://www.nbrp.jp/
[3] "Deposit": 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 deposit 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 variousdatabases designated by AMED, including in response to the above.

12. Regarding the Encouragement of Shared Use of Research Equipment

From the perspective of the efficient use of contracted R&D funds and the effective use of research equipment, joint use of research equipment and combining research funds for multiple projects based on certain requirements are permitted. Details should be confirmed with the AMED "Administration Manual for Contracted R&D Agreement."*

* Link from https://www.amed.go.jp/keiri/index.html

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) or teaching assistants (TA) 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 or TAs, 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. 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 MEXT Public Research Funds"* (formulated on December 20, 2011 by MEXT's Science and Technology Academic Council's Personnel Committee), "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.

* "Basic Policy on Support for Diverse Career Paths for Young Postdoctoral Fellows to Be Employed through MEXT Public Research Funds" (formulated on December 20, 2011 by MEXT's Science and Technology Academic Council's Personnel Committee) http://www.mext.go.jp/b_menu/shingi/gijyutu/gijyutu10/toushin/1317945.htm

15. Responding to the Implementation of the Clinical Research Act

As the Clinical Research Act went into effect (on April 1, 2018), a number of new actions became necessary in order to conduct clinical research, such as registration with the Japan Registry of Clinical Trials (jRCT) database established by the Ministry of Health, Labour and Welfare and the reporting of diseases and the like. Please take the appropriate action to ensure compliance with the Act.

Clinical research initiated after the Clinical Research Act goes into effect should not be redundantly registered in the databases of Japanese clinical research registration institutions other than the jRCT. If the research has already been registered in the database of another clinical research registration institution in accordance with the "Ethical Guidelines for Medical and Health Research Involving Human Subjects," please take the appropriate action in accordance with laws and regulations, etc.

For more details of responding to the implementation of the Clinical Research Act please refer to the Ministry of Health, Labour and Welfare (MHLW) website.*

* Regarding the Clinical Research Act (Ministry of Health, Labour and Welfare website) http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000163417.html

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 "Calls for Proposals,"[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] https://www.amed.go.jp/en/news/proposals.html

Content of inquiry	Contact address
R&D projects being solicited; review; how to fill in proposal documents	Division of Emerging Research, Department of Research Infrastructure, AMED Tel: +81-3-6870-2224 E-mail: kenkyuk-kobo"AT"amed.go.jp
Misconduct/fraudulent use/fraudulent receipt	Department of Research Integrity and Legal Affairs, AMED E-mail: kouseisoudan "AT"amed.go.jp
Management of conflict of interest/research ethics education programs	Department of Research Integrity and Legal Affairs, AMED E-mail: kenkyuukousei"AT"amed.go.jp
RIO Network	Department of Research Integrity and Legal Affairs, AMED E-mail: rionetwork"AT"amed.go.jp
Medical IP Desk (Contact point for medical IP consultation)	Department of Intellectual Property, AMED E-mail: medicalip"AT"amed.go.jp
Support provided by the AMED Drug Discovery Support Network/Department of Innovative Drug Discovery and Development	Department of Innovative Drug Discovery and Development East Japan Office, AMED 8F Muromachi Chibagin Mitsui Bldg, 1-5-5 Nihonbashi-Muromachi, Chuo-ku, Tokyo 103-0022, Japan Tel: +81-3-3516-6181 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. ・After checking the FAQ page, log in to e-Rad (https://www.e-rad.go.jp/contact.html) so that you can check the operation manual, then dial: Tel: 0570-066-877 (NAVI-DIAL) or +81-3-6631-0622 (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	Japan Science and Technology Agency (JST) National Bioscience Database Center Tel: +81-3-5214-8491 E-mail: nbdc-kikaku"AT"jst.go.jp

XI. R&D Projects Being Solicited

The R&D project 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 “Molecular understanding of the biological phenomena and responses at the early life stages to improve the quality of health and medical care” (page 54)

1. Understanding of the biological phenomena and responses at the early life stages to improve the quality of health and medical care

Program Supervisor (PS): Hiroyuki Sasaki, Distinguished Professor, Medical Institute of Bioregulation, Kyushu University
Program Officer (PO): Hiroyuki Takeda, Professor, Graduate School of Science, the University of Tokyo

Outline of the Research and Development Area

The goal of this R&D area is to develop a comprehensive understanding of various biological phenomena in the early stages of life (between fertilization and young adulthood) and the effect environmental factors have on the body during that period for better health and medical care in the future.

Over the past decade, we have come to understand that various biological and environmental factors are involved in health and disease at the early stages of life. Those include malnutrition during pregnancy and lower birthweights, brain dysfunction in part caused by developmental disorders or disabilities, weight loss or obesity during young adulthood due to inadequate/excessive nutritional intake, immune diseases such as allergy, or problems relating to reproductive health that affect the number of births or the health of the next generation. There have also been a series of papers suggesting that these factors could be risk factors for disease during middle-to-late stages of life (from adulthood into old age) and that the risk factors can even be passed on to subsequent generations. Research focusing on the early stages of life is expected to contribute to improved quality of life (QOL) across all stages. However, there has not been enough research conducted on biological responses in the early stages of life due to the complexity of the study subjects, difficulties in approaching the targets, and the amount of time needed for this research.

Tremendous progress has been made, however, in the development of more sophisticated omics and imaging technologies, and in various research fields including developmental biology, metabolism, immunology, and neuroscience. Researchers in Japan and overseas have started to systematically gather basic information from various model animals or data/samples from human birth cohorts and are developing platforms for integrated research. The research on the early stages of lie should benefit from these progresses and it now seems possible to trace the impact of environmental factors and disease risks from the early stages of life through to the next generation.

In order to develop an understanding of biological phenomena and responses at the early life stages, this R&D area will bring together and promote interactions between researchers from diverse fields, including basic biology, medical science, agriculture, engineering, and informatics. This R&D area also aims to establish analytical technology platforms to deepen our understanding, develop applications for these technology platforms, and discover new control technology seeds.

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

For this R&D area, we invite proposals focusing on the development of a fundamental understanding of various biological phenomena at the early life stages and of a quantitative understanding of the impact of early exposure to environmental factors by combining a wide range of methods, including omics, imaging, and mathematical/data analysis. With this, we hope to generate seeds for better health and medical care in the future. Specific goals are as follows: (1) Improve our understanding of the biological phenomena and responses at the early stages of life and clarify the molecular mechanisms involved, (2) establish platform technologies to enable high-precision measurements that can be applied to the studies on the early stages of life and develop their applications, and (3)

identify key response factors at the early stages of life and generate seeds for preventive, diagnostic, and therapeutic technologies.

(1) AMED-CREST (unit-type)

For this R&D area, we invite proposals for innovative basic research with a multidisciplinary approach to improving our quantitative understanding of the biological phenomena and responses at the early stages of life and clarifying the mechanisms involved. We also invite proposals for research into biomarkers to evaluate biological responses or the discovery of platform technology seeds for the regulation of these responses.

Ideally the research will combine a number of different research fields into a single research unit in order to be able to understand and control complex biological phenomena and responses at the early life stages. We welcome proposals from researchers who collaborate actively with other research groups in different fields during the course of their research.

Below we provide examples of possible proposals, but we are looking for innovative research proposals that go beyond these examples.

- Understand the mechanisms underlying biological responses at the early stages of life in animal models and humans
- Clarify the mechanisms by which biological responses at the early stages of life have an impact on health at the middle-to-late stages of life and in subsequent generations
- Develop more sophisticated multi-omics and imaging technologies and develop applications for cohort samples etc.
- Obtain spatiotemporal data using model animals, organoids, etc. and develop comprehensive analytical technologies
- Explore and identify diagnostic markers and intervention targets for diseases caused by factors in the early stages of life
- Discover technology seeds for interventions (e.g., nutrients, drugs) for diseases caused by factors in the early stages of life
- Develop technologies for the precise control of epigenomic status or protein functions that are potential interventional targets

We do not require the participating researchers in the applications to be currently engaged in research into the early stages of life. We welcome innovative new proposals from different research fields as long as they are scientifically reasonable.

We will select approximately 3–6 proposals for AMED-CREST this fiscal year, with a total budget of up to 300 million yen per project for R&D costs (direct costs) over the project term.

(2) PRIME (solo-type)

The PRIME program involves research performed by an individual researcher. We invite proposals in the R&D areas as described in the AMED-CREST program, particularly for highly innovative research. We welcome proposals for challenging programs that could lead to new breakthroughs or develop novel technologies that may contribute to basic research of this R&D, i.e. the mechanisms of biological responses at the early life stages or the mechanisms that trigger changes in traits and disease over time (for example, discovery of new animal models or experimental systems or imaging technologies that allow minimally invasive evaluation of biological responses).

In addition to the research applicant who has a particular specialty directly related with the early stages of life, we will also consider the applicant in related fields who will actively develop a network through collaborations with other research groups in the same or different fields, particularly other AMED-CREST research units, for the future application of their research outcomes.

We will select approximately 8–12 proposals for PRIME this fiscal year, with a total budget of up to 40 million yen per project for R&D costs (direct costs) over the project term.

Briefing of Solicitation for this research area is planned as following date. (NOTE: only in Japanese.)
Date: April 25 (Thursday) 13:40 - 14:20
In detail, please refer “III. 2. (5) Schedule for Briefings of Solicitation.”

○ R&D Area for the Research and Development Objective: “Investigations into life phenomena and the discovery of medical technology seeds based on spatiotemporal insights into biological tissue adaptation and repair mechanisms” (page 57)

2. Understanding of pathophysiological processes and discovery of medical technology seeds through spatiotemporal research of tissue adaptation and repair mechanisms

Program Supervisor (PS): Akihiko Yoshimura, Professor, Keio University School of Medicine
Program Officer (PO): Takehiko Yokomizo, Professor, Juntendo University School of Medicine

Outline of the Research and Development Area

The goal of this R&D area is to significantly accelerate the discovery of technology seeds that contribute to health and medical care by deepening the spatiotemporal understanding of biological tissue adaptation and repair mechanisms.

The body maintains its functions through tissue adaptation and repair against various types of tissue injury or excessive organ stress. However, when the control mechanisms for adaptation and repair break down, tissue homeostasis starts to fail and eventually leads to the onset of serious diseases. For example, tissue fibrosis which is often observed in diseases of the kidney, liver, or heart, etc. is caused by degenerative changes in the tissues due to dysfunctions of the tissue adaptation and repair mechanisms. It is now becoming clear that many neurodegenerative diseases and lifestyle diseases induced by tissue degeneration are triggered or exacerbated by inflammation or effects from other organs.

We therefore need to elucidate the mechanisms by which tissue adaptation and repair systems are maintained or break down, including not only local tissue events but also interactions between organs, tissues, or cells. We are expected to establish effective methods for treatment or prevention of the diseases by using such findings.

We do not currently have a full understanding of how the body responds to the damage received from the inside and outside of the living body, what types of cells in the tissues are involved in, and what type of mechanisms proceed over time. We also do not have a sufficient understanding of the interactions between organs. One challenge for the future is to elucidate the mechanisms that control regeneration by tissue stem cells or blood vessel remodeling within an injured organ. In order to investigate these extremely complex biological phenomena, we need to bring together the researches that have been conducted separately in the fields of immunology, embryology/regeneration, neurology, metabolism, and endocrine systems in order to drive further development of a new field of research which uncovers the biological tissue adaptation and repair mechanisms.

In this R&D area, we aim to elucidate the mechanisms by which tissue adaptation and repair systems are maintained or break down. We will attempt to establish and apply analytical technologies to allow greater spatiotemporal insights and to use the findings obtained in this field to discover the seeds for preventive, diagnostic, and therapeutic technologies.

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

The aim of this R&D area is defined as elucidating at the molecular and cellular level according to time and location the mechanisms by which tissue adaptation and repair systems are maintained or break down, and to use these findings in the discovery of new health and healthcare technology seeds.

For that purpose, we believe that the research should deepen our integrated understanding of the biological control systems that comprise interactions between multiple cells and organs, rather than narrowing down to single cell or gene. We will engage in R&D that combines research from various fields (such as immunology, brain/nerves, embryology/regeneration, metabolism, and endocrinology) and use cutting-edge technologies (such as technologies for gene sequencing, omics, single cell analysis, or organoids).

We also think it is important to improve our understanding of the spatiotemporal mechanisms by which tissue adaptation and repair systems are maintained or break down. Important research themes will include in-depth analyses of the processes involved in pathological changes at the molecular and cellular levels over the period of time from a healthy state to the onset of tissue injury or degeneration and disease or remodeling until a steady state is re-achieved. Another important theme is research using imaging and other technologies to investigate dynamic pathological change in the body.

For this R&D area, we invite proposals focusing on the dynamic morphological changes caused by complex interactions between cells or between organs that aim to uncover the true nature of tissue adaptation and repair mechanisms and to discover health and healthcare technologies. We prioritize research that provides a better understanding of the biochemistry and pathology involved, in terms of molecules, substances, or gene expression,

rather than simple phenomena. This category includes the discovery of new cells involved in a particular phenomenon, physiologically active substances, or novel mechanisms.

(1) AMED-CREST (unit-type)

For this R&D area, we will accept innovative basic research proposals that will elucidate the mechanisms by which tissue adaptation and repair systems are maintained or break down and that will lead to the discovery of new health and healthcare technology seeds. We will also accept proposals on research into the establishment and development of technologies for spatiotemporal analysis of biological tissue adaptation and repair mechanisms and research aimed at using these control mechanisms to discover seeds for preventive, diagnostic, and applied technologies.

We welcome proposals that will combine multiple biological regulatory systems in order to further our understanding of the extremely complex life phenomena involved in tissue adaptation and repair mechanisms. To achieve this, we welcome proposals from research teams that combine work from a number of different research fields into a single research unit. We also welcome a single group headed by the leading investigator who can link across different fields. Note that the mix of programs selected will take into account the balance of fields within the research area.

Below we provide examples of possible R&D proposals, but we are looking for innovative research proposals that go beyond these examples

- Elucidate the mechanisms by which tissue adaptation and repair mechanisms are maintained or break down using animal disease models or human disease samples. Elucidate tissue adaptation and repair mechanisms that involve spatiotemporal interactions (relating to biological control systems) between cells, tissues or organs mediated by physiologically active substances or nervous/immune systems. The research should not aim to just describe a phenomenon, but should include identification of the genes, molecules, substances, and cells responsible for specific interactions and aim to elucidate the control mechanisms governing these factors.
- Develop new methods for the analysis of processes including pathological changes over time at the molecular and cell levels that elucidate the mechanisms of the maintenance of tissue adaptation and repair and the breakdown to the onset of disease and establish novel concepts for the mechanisms of tissue adaptation and repair. For example, analysis using cutting-edge imaging technologies; bioinformatics, including comprehensive omics analysis or single cell gene expression analysis; genome-wide Assay for Transposase Accessible Chromatin (ATAC) sequencing; or chromatin immunoprecipitation (ChIP) sequencing.
- Develop and establish complex organoids featuring both various cell types (parenchymal/stromal cells, stem cells, immune cells, nerve cells) and the niche environments in which these cell types are found (e.g., blood vessels, lymphocytes, peripheral nerves). Use these organoids to establish experimental model systems of tissue adaptation and repair that reproduce human disease states and physiological responses, and apply these systems therapeutically.
- Research using model animals where genetic analysis is easily applicable. Ideally the proposal would include further development into mammals.
- Elucidate the significance of tissue stem cell regeneration and repair in response to injury in various organs (skin, bone marrow, cerebrospinal, or nervous system) and therapeutic applications.
- Research focused on metabolism within tissues and the body as a whole accompanying aging or obesity.
- Elucidate acute and chronic inflammation and the role of acquired immunity in the process of tissue repair or remodeling after tissue injury.

We do not require the participating researchers in the applications to be currently engaged in research into tissue adaption and repair mechanisms. We welcome innovative new proposals from different research fields as long as they are scientifically reasonable. We also require clarification on whether intellectual property rights on the research outcomes can be secured, because this is important when developing novel health and healthcare technologies in the future.

We will select approximately 3-5 proposals for AMED-CREST this fiscal year, with a total budget of up to 300 million yen per project for R&D costs (direct costs) over the project term.

(2) PRIME (solo-type)

The PRIME program involves research performed by an individual researcher. We invite proposals in the R&D areas as described in the AMED-CREST program, particularly highly innovative research conducted by young

researchers. We welcome proposals for challenging programs that could lead to new breakthroughs or research that could develop completely new technologies that may contribute to basic research to develop insights into tissue adaptation and repair mechanisms. For example, as well as the examples provided in the AMED-CREST section, we will consider research that utilizes model organisms with a high tissue regeneration ability; elucidates the significance of as yet unknown phenomena involved in, or cells that contribute to, tissue remodeling; investigates tissue adaptation and repair mechanisms using gene expression profiling or mathematical modeling; discovers novel physiologically active substances involved in tissue injury and repair; uses lipidomics and omics analysis; elucidates the significance of acquired immunity; or develops new technologies that promote tissue repair.

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. As with AMED-CREST, we are also looking for intellectual property rights on the research outcomes to be secured, because this is important when developing novel health and healthcare technologies.

We will select approximately 8-12 proposals for PRIME this fiscal year, with a total budget of up to 40 million yen per project for R&D costs (direct costs) over the project term.

Briefing of Solicitation for this research area is planned as following date. (NOTE: only in Japanese.)
Date: April 25 (Thursday) 14:30 - 15:10
In detail, please refer “III. 2. (5) Schedule for Briefings of Solicitation.”

○ R&D Area for the Research and Development Objective: “Clarification of the mechanism of individual functional impairment over the entire life course” (page 60)

3. Clarification of the mechanisms of individual’s functional impairment over the entire life course

Program Supervisor (PS): Eisuke Nishida, Director, RIKEN Center for Biosystems Dynamics Research (BDR)
Program Officer (PO): Eiji Hara, Professor, Research Institute for Microbial Diseases (RIMD), Osaka University

Outline of the Research and Development Area

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, and epigenetics, we will seek cooperation in a wide range of research fields including nutrition, hygienic environment, sleep and circadian rhythms, and particularly in mathematical engineering and chemical biology. 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.

- Discover technologies to analyze individual functional impairment, using system biology approaches
- Discover technologies to regulate individual functional impairment, using chemical biology methods
- Develop indicators to evaluate individual functional impairment
- Discover platform technologies to regulate individual functional impairment
- 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 specific organ functional impairment on the individual as a whole
- Analysis of the effect of circadian rhythm and sleep on individual functional impairment

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 2-4 proposals for AMED-CREST this fiscal year, with a total budget of up to 300 million yen per project for R&D costs (direct costs) over the project term.

(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 40 million yen per project for R&D costs (direct costs) over the project term.

Briefing of Solicitation for this research area is planned as following date. (NOTE: only in Japanese.)
Date: April 25 (Thursday) 15:10 - 15:50
In detail, please refer for this research ae for Briefings of Solicitation."

XII. (Reference) Research and Development Objectives

1. **Research and Development Objective**: Molecular understanding of the biological phenomena and responses at the early life stages to improve the quality of health and medical care

1. Objective Title

Molecular understanding of the biological phenomena and responses at the early life stages to improve the quality of health and medical care

2. Overview

A series of papers have been published over the last decade suggesting that health is affected by various environmental factors during the early stages of life (between fertilization and early adulthood), that their early exposures could be risk factors for disease during middle-to-late stages of life (from adulthood into old age), and that disease risk factors can be passed on to subsequent generations. Research focusing on the early stages of life is expected to contribute to improved quality of life (QOL) across all stages. Although this is an important area for study, there has been limitations in research conducted on biological responses in the early stages of life, due to the complexity of the study subjects, difficulties in approaching the targets, and the amount of time needed for this research.

There have been astonishing progresses in recent years in the development of more sophisticated omics and imaging technologies, and in various research fields including developmental biology, metabolism, immunology, and neuroscience. Researchers in Japan and overseas have started to systematically gather basic information from various model animals or data/samples from human birth cohorts and are developing platforms for integrated research aimed at understanding of the biological phenomena at the molecular level during early life stages, the mechanisms involved, and the impact of environmental factors from the early stages of life through to the next generation. As such, this R&D objective is aimed at more comprehensive understanding of the impact on the body from environmental factors at the early stages of life by combining diverse approaches of biology and medical science, agriculture, engineering, and informatics. In the future, we hope that this research will provide evidence to underpin the development of more sophisticated preventive interventions and therapeutic technologies and to contribute to better quality health and medical care (including maternal and child health).

3. Goals and Objectives

This R&D objective aims to deepen our understanding of the various issues in early life stages and to generate seeds for better health and medicine in the future by combining a wide range of methods, including omics, imaging, and mathematical/data analysis, to gain a quantitative understanding of the impact of early exposure to various environmental factors on life at later stages.. Specific goals are as follows:

(1) Understanding: Improve our understanding of the biological phenomena and responses at the early stages of life and clarify the molecular mechanisms involved
(2) Technology: Establish platform technologies to enable high-precision measurements that can be applied to the studies on the early stages of life and develop their applications
(3) Control: Identify key response factors at the early stages of life and generate seeds for preventive, diagnostic, and therapeutic technologies

4. Future Vision for Society That Should Be Taken into Account in the Research

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

- We can become a healthy and sustainable society if we can overcome a range of issues relating to maternal and child health and the birth of the next generation (including infertility or low birth weights).
- Our society can achieve a revolution in healthcare if we can take a preemptive-healthcare approach against various diseases (including developmental disorders, lifestyle-related disease, and allergies) where effective interventions can be made in the early stages of life and overcome diseases even after onset.

- We can become a society where there are accelerating improvements in lifestyle habits and the environment due to the dissemination of evidence-based guidelines etc., and where various diseases can be prevented, healthy lifespans can be extended, and the social security burden can be reduced.
- Our industries can become more competitive if we apply the seeds generated through this research to the further development of the health industry (such as nutritional foods) and drug development.

5. Specific Research Examples

(1) Understanding: Improve our understanding of the biological phenomena and responses at the early stages of life and clarify the molecular mechanisms involved
- Understand the mechanisms underlying biological responses to environmental factors at the early stages of life (from fertilization to young adult) in both animal models and humans (including clarification of the corresponding basis for physiological homeostasis), by combined approaches of developmental biology, metabolism studies, immunology, and neuroscience.
- Clarify the mechanisms by which biological responses at the early stages of life have an impact on wellbeing and disease at the middle-to-late stages of life and how the health of subsequent generations is affected

(2) Technology: Establish platform technologies to enable high-precision measurements that can be applied during the early stages of life and develop their applications
- Develop analytical systems using animal models or human stem cells/organoids, long-term imaging technologies, or single-cell omics, and applications for cohort samples etc.
- Develop applications for integrative analysis of multi-omics data and imaging, higher-level mathematical modelling, or disease prognoses

(3) Control: Identify key response factors at the early stages of life and generate seeds for preventive, diagnostic, and therapeutic technologies
- Identify biomarkers and intervention targets (e.g., disease-causing molecules) that could be used to prevent, diagnose, or treat diseases caused by factors in the early stages of life and discover technologies for interventions (e.g., nutrients, drugs)
- Develop technologies for the precise control of epigenomic status (e.g., methylation) or the functioning of enzymes/proteins that are potential interventional targets

6. Domestic and International Research Trends

Domestic trends

Research is actively underway to further our understanding in various different fields, including epigenomic research and technology development in reproduction and ontogeny under the AMED-CREST Epigenome R&D area; tissue/organ research including from a pathological perspective under the AMED-CREST/PRIME Adaptation and Repair R&D area; research from the perspective of immunity and metabolism under the AMED-CREST/PRIME Microbiome and AMED-CREST Disease Metabolism R&D areas; and research with a focus on the entire life course under the AMED-CREST/PRIME Functional Impairment R&D area. Japan is a global leader in key fields of research aimed at understanding biological responses and the phenomena of life at the early stages of life, particularly in ontogeny, immunity, and stem cells and in areas like platform technologies for imaging or omics analysis.

As well as developments in these fields of research and technology, scientists are getting closer to understanding the intrinsic nature of complex life phenomena, such as dynamic changes in biomolecules in response to environmental factors, as a result of significant developments in technologies including genome editing in model animals or the creation of organoids using human cells. Other areas of note include the increasing opportunities for integration of various birth cohorts in Japan and the existence of a three-generation cohort from the Tohoku Medical Megabank Organisation (ToMMo) at Tohoku University. Japan is particularly skilled at basic research and has established an environment that supports the validation of hypotheses obtained through this basic research, which will contribute to the discovery of new medical findings and technology seeds for health and healthcare.

International trends

More and more papers are being published on the results of birth cohort research over the past 50 years or more in the UK, Holland, and elsewhere, with the results supporting a relationship between the environment in the early stages of life and development/growth, as well as with subsequent disease in the life stages from adulthood into old age. The rapid developments in epigenomic and metabolomic analytical technologies in the 2010s have resulted in

epidemiological findings as well as a better understanding of the mechanisms involved at a molecular level. As a result, various R&D programs in Europe and the US, for example at the National Institutes of Health (NIH) in the US, have been initiated to better understand and attempt to control various phenomena at the early stages of life (including metabolism, nutrition, immunity, microbiomes, reproduction, and ontogeny).

7. History of the investigations

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

1. Analysis materials were created using the Grants-in-Aid for Scientific Research (Kakenhi) database and other sources to analyze research trends in Japan as well as a database on research papers. These materials were used to run a questionnaire-based survey of key research trends that was submitted to the specialists participating in the specialist network of the National Institute of Science and Technology Policy's (NISTEP) Science and Technology Foresight Center, each of the units at the Japan Science and Technology Agency (JST) Center for Research and Development Strategy (CRDS), and the Program Directors at the Japan Agency for Medical Research and Development (AMED).
2. The responses from these questionnaires, as well as information from interactions with experts and a strategic proposal developed by JST-CRDS entitled "Proposal for Issue-driven Research and Development III: Promoting Life Course Health-care—Importance of Preemptive Medicine in Pregnancy to Childhood," highlighted the significance of the prevention of various disease types in the time between fertilization and early childhood and the growing need for basic research. "Understanding the signaling system for mother-child interactions through transdisciplinary approach was specified as a key research trend
3. In November 2018, the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and AMED co-hosted a workshop that brought together 18 experts from the relevant industries and academia to build a concrete strategy. Discussions covered 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

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

Introduction

… the translation of Japan's basic scientific research into efforts to promote the development of the world's most advanced medical technology and the extension of healthy life expectancy through medical care that utilizes the results of these efforts is a pressing issue, as is the need to ensure the sustainability of Japan's health care system. Moreover, it would be fair to say that medical care initiatives focused on the children who will support our society in the future are currently inadequate.

I-1-(1)-(b)

… Accordingly, in addition to preemptive medicine, such as measures undertaken before onset, there is a need to strengthen evidence-based medical care as far as possible, and to implement appropriate initiatives focused on needs that are currently not being served or are not adequately served with the drugs and medical devices available today.

G7 Ise-Shima Vision for Global Health (27 May 2016)

2-2-2

4) Recognize that disease prevention and healthy living at all stages of life play a key role in active ageing and that primary prevention starts at the beginning of life.

9. Miscellaneous

We expect synergies from the linking of this R&D objective with research under the AMED-CREST Functional Impairment R&D area. We also hope to promote more efficient and effective research by linking with research institutes, academic societies, consortia, and other bodies in Japan and overseas, and to accelerate progress through joint research programs and other initiatives.

2. Research and Development Objective: Investigations into life phenomena and the discovery of medical technology seeds based on spatiotemporal insights into biological tissue adaptation and repair mechanisms

1. Objective Title

Investigations into life phenomena and the discovery of medical technology seeds based on spatiotemporal insights into biological tissue adaptation and repair mechanisms

2. Overview

The body protects itself from various in- and ex-vivo stimuli by controlling adaptation and repair mechanisms (remodeling) at a tissue level over time; if this series of mechanisms breaks down, tissue functions fail. For example, we now know that progressive fibrosis can trigger diseases of the kidney, liver, and heart that have started to become major issues for society today. It is also becoming apparent that many neurodegenerative diseases and lifestyle diseases are triggered or exacerbated by inflammation or effects from other organs. There are no effective treatments for these types of diseases, so there are significant unmet medical needs. Researchers have found it difficult to fully uncover the mechanisms at play because they involve such complex biological phenomena. Japan is a global leader in fields focusing on the various biological control systems (including immunology, ontogeny/regeneration) and cutting-edge technologies (such as imaging, organoids) relevant to tissue adaption/repair mechanisms.

This Research and Development Objective focuses on the dynamic morphological changes (pathological changes over time) caused by complex interactions between cells or between organs, with the goal of narrowing down the underlying characteristics of tissue adaptation and repair mechanisms and achieving a significant acceleration in the discovery of health care and medical technology seeds.

3. Goals and Objectives

This Research and Development Objective aims to achieve a much deeper understanding of biological phenomena and disease and to discover health care and medical technologies by getting to the heart of the complex and unexplained biomaintenance systems of tissue adaptation and repair mechanisms.

The goal is to accelerate the development and application of cutting-edge technologies (such as 4D imaging and organoid technologies) in fields relevant to biocontrol systems (such as immunology, ontogeny/regeneration, neurology, metabolism, and endocrinology), overcoming the boundaries between each field, and coordinating strategies between multiple fields of research. We define the following targets to be achieved:

(1) Clarify the mechanisms of maintenance and breakdown involved in biological tissue adaptation and repair
(2) Establish and apply/develop 4D (spatiotemporal) analytical technologies for biological tissue adaptation and repair mechanisms
(3) Identify control factors for biological tissue adaptation and repair mechanisms and identify seeds for preventive, diagnostic, and therapeutic technologies

4. Future Vision for Society That Should Be Taken into Account in the Research

The research will help us to develop a society as outlined below by achieving the items described in section 3. Goals and Objectives.

Society that can achieve medical breakthroughs, such as methods to overcome diseases caused by errors arising in the tissue adaptation and repair mechanisms [e.g., diseases like chronic kidney disease (CKD), non-alcoholic steatohepatitis (NASH), chronic obstructive pulmonary disease (COPD), or heart disease that are caused by progressive fibrosis]

Society with longer healthy lifespans and a reduced social welfare burden (such as spending on healthcare and long-term nursing care) through the development of technologies that can prevent end-stage renal disease (dialysis) due to CKD progression results or liver cancer due to disease progression in the liver.

Society with vigorous domestic industries through the use of tissue adaption and repair mechanisms in healthcare industries (such as nutrients/ foods, cosmetics)

5. Specific Research Examples

(1) Clarify the mechanisms of maintenance and breakdown involved in biological tissue adaptation and repair

Clarify tissue adaptation and repair mechanisms through an understanding of spatiotemporal interactions (related to biological control systems) between various types of cells and molecules (e.g., immune cells, tissue stem cells) or between tissues and between organs. When conducting this research, apply genome editing, single cell analysis,

or organoid technologies, and perform comprehensive analyses as necessary of animal models or organisms with high regenerative capabilities.

(2) Establish and apply/develop 4D (spatiotemporal) analytical technologies for biological tissue adaptation and repair mechanisms

Establish and apply/develop model experimental systems (e.g., human organoids) of tissue adaptation and repair that are precisely reproducible for the human pathology or physiological responses.

In addition, develop and apply technologies (e.g., 4D dynamic imaging technologies, cell lineage analysis technologies) to accelerate complex in vivo crosstalk analyses in the tissue adaptation and repair mechanisms.

(3) Identify control factors for biological tissue adaptation and repair mechanisms, and identify seeds for preventive, diagnostic, and therapeutic technologies

Discover technology seeds for evaluation/diagnosis of pathological processes in tissue adaptation and repair; discover preventive/therapeutic technology seeds based on analysis of pathological processes in tissue adaptation and repair; and validate this research using human samples.

6. Domestic and International Research Trends

Domestic trends

Thus far, Japan has conducted world-class research into individual biological control systems, through the Grants-in-Aid for Scientific Research on Innovative Areas that included “Regulation of polarity signaling during morphogenesis, remodeling, and breakdown of epithelial tubular structure (2011–15)” to promote research into 3D mechanisms of tissue formation and maintenance and “Analysis and synthesis of multi-dimensional immune organ network (2012–16)” to promote multi-dimensional research, with a focus on immune cells. In addition, the Japanese Society of Inflammation and Regeneration and other medical societies aim to understand tissue adaptation and repair mechanisms from a wide-ranging perspective, encompassing inflammation (immune systems) and regeneration (ontogeny, regenerative systems), as well as metabolic systems, nervous systems, and even endocrine systems. At medical societies focused on conventional basic systems (such as immunology, ontogeny/regeneration, nerves, metabolism, endocrinology) and at medical societies that look at clinical aspects by organ or disease, we are seeing more research that combines multiple biocontrol systems in a bid to understand tissue adaptation and repair mechanisms. In the AMED-CREST R&D Area of “Innovation for ideal medical treatment based on the understanding of maintenance, change and breakdown mechanisms of homeostasis among interacting organ systems (2012–19),” research is underway to understand the mechanisms involved to maintain homeostasis through interactions between different organs or tissues, and we expect synergistic effects because of the relationship between our R&D objectives that aim to elucidate pathological processes in tissue adaptation and repair mechanisms. From a technology perspective, Japanese industry and academia boast world-class imaging technologies, Japanese organoid technologies are the most advanced in the world, and Japan’s 3D culture/structure technologies have improved so much that they are now being used in research into biological phenomena. Leading scientists already working in these research and technology fields are starting to produce results that are relevant to the focus of this R&D Objective, so the time seems right for top-down investments into R&D on this theme.

International trends

Research and development has taken off around the world into the tissue adaptation and repair mechanisms that are the target of these R&D Objectives. For example, there appears to have been a rapid increase in the number of presentations in this field given at international conferences, such as the Keystone Symposia meetings that gather leading researchers from around the world to discuss hot topics in the life sciences, and global research communities are focusing their efforts on tissue adaptation and repair mechanisms. We are also starting to see some Japanese researchers involved in these international conferences.

The biggest trend today, and one that is arguably the pinnacle of morphology and pathology research, is the work currently underway, particularly in the US and UK, to create a Human Cell Atlas, with the goal of mapping all the cells found in tissues and organs and to ultimately explain the entire human body at the cellular level. The Chan Zuckerberg Initiative (CZI) plans to invest around 60 billion yen over a ten-year period and the National Institutes of Health (NIH) Common Fund plans to invest 600 million yen each year. Over the longer term, we expect this to provide a platform for all types of life sciences research.

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 "Investigations into biological phenomena and the discovery of medical technology seeds based on spatiotemporal insights into biological tissue adaptation and repair mechanisms" was specified as a key research trend.

Workshops and creation of R&D objectives

A workshop was held where experts from academia and the industries relevant to the key research trend of "Investigations into biological phenomena and the discovery of medical technology seeds based on spatiotemporal insights into biological tissue adaptation and repair mechanisms" 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. 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 Healthcare Policy (Cabinet decision dated 22 July 2014, partially revised on 17 February 2017)

Chapter 2. (1) 1)

⋯ the government will promote the use of Japan's advanced science and technology to identify the clinical nature of diseases … It will also cultivate groundbreaking new seeds that offer substantial hope for future drugs, medical devices, and medical technology, including the development of … innovative drugs and medical devices, etc.

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

I. 1. (1) (a)

Health and disease are not necessarily discrete states, so rather than providing treatment-focused medical care alone, it would be preferable to attach greater importance to measures for extending healthy life expectancy through research on disease prevention and initiatives that employ appropriate measures for preventing the onset, complication, and exacerbation of conditions though disease projections with a high level of probability, and early diagnosis before patients actually become unwell.

Growth Strategy 2017 (Cabinet decision dated 9 June 2017)

Chapter 2 I. 1. (2) iii)

The government will also advance the research and development of biomarkers and risk markers that allow symptoms of lifestyle diseases and dementia to be detected, at the same time verifying the usefulness of the biomarkers developed. The government will also advance the research and development of pharmaceuticals and other items that are expected to be utilized for the prevention of lifestyle diseases and dementia.

9. Miscellaneous

In terms of programs relevant to this Strategic Objective, AMED-CREST is running the program "Innovation for ideal medical treatment based on the understanding of maintenance, change and breakdown mechanisms of homeostasis among interacting organ systems," which covers an extremely wide range of research into the maintenance and breakdown mechanisms involved in homeostasis. However, this Strategic Objective proposal has a particular focus on adaptation and repair mechanisms at the biological tissue level. As an international strategy, we look for research to progress in an efficient and effective manner, for example through a proactive approach to joint research, with the formation of international consortia bringing together a diverse range of researchers from Japan and overseas.

3. 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.

Japan Agency for Medical Research and Development

Division of Emerging Research, Department of Research Infrastructure

Japan Agency for Medical Research and Development (AMED)
21F Yomiuri Shimbun Bldg., 1-7-1 Otemachi, Chiyoda-ku, Tokyo, JAPAN. 100-0004
Tel: +81-3-6870-2224 Fax: +81-3-6870-2246

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