FY2023

Advanced Research and Development Programs for Medical Innovation

Application Guidelines

April 2023

Division of Innovative Research and Development
Department of Innovation and Clinical Research Center
Japan Agency for Medical Research and Development (AMED)

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Chapter 1. Introduction

These Application Guidelines specify the conditions and solicitation details regarding the unit-type (AMED-CREST) and solo-type (PRIME) R&D projects being solicited among the types of R&D projects under Advanced Research and Development Programs for Medical Innovation, which is administered by the Japan Agency for Medical Research and Development (hereinafter referred to as "AMED").

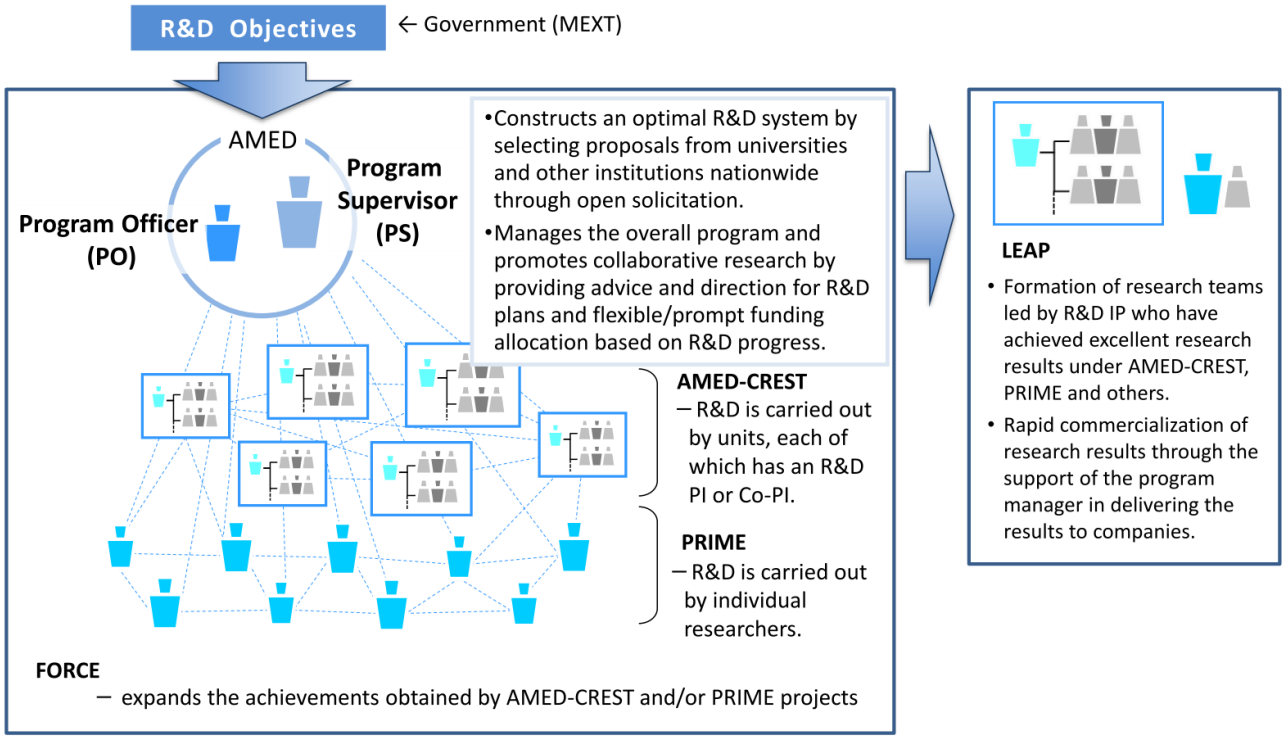
1.1 Program Outline

1.1.1 Current Status of Program

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 innovative seeds, while also accelerating and deepening R&D that yields promising results.

This program comprises four types of research: unit-type (AMED-CREST), solo-type (PRIME), incubation-type (LEAP), and step-type (FORCE). For AMED-CREST and PRIME, under the R&D objectives determined by the national government, AMED specifies the R&D areas to be pursued and the Program Supervisors (PS) and Program Officers (PO) in charge of the R&D areas. 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 aims to swiftly realize practical application of research achievements that are promising but for which it is difficult at the present for companies, etc., to assess risk. FORCE promotes research that can be expected to produce significant achievements and developments through additional support for completed AMED-CREST, PRIME and other R&D projects with the aims of verifying disease association using human disease samples as well as the versatility of developed analysis methods and measurement devices.

LEAP and FORCE are not included in the scope of this solicitation.



1.1.2 Program Direction

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 check Chapter 3 for further details.

Program	R&D Period	R&D Costs (entire direct cost)
Unit type (AMED-CREST)	Up to five-and-a-half years	150 to 500 million yen per R&D project
Solo type (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 indirect costs of up to 30% of R&D costs (direct costs) shown in the table above.

Message from the President of AMED

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 dynamic 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 and Program Officers 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 areas in the program are 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. R&D areas are jointly managed by AMED-CREST and PRIME, 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 submit proposals to PRIME with a view towards achieving sustainable development into the future 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.

MISHIMA Yoshinao, Ph.D.

President, Japan Agency for Medical Research and Development

1.2 Program Structure

1.2.1 Program Implementation System

In accordance with the Japanese government's Plan for Promotion of Medical Research and Development,* AMED promotes R&D centering on the six integrated projects of drug discovery and development; medical devices and healthcare; regenerative medicine and cell and gene therapies; genomic medicine; basic medical research; and translational and clinical research centers. To ensure efficient utilization of competitive research funds and generation of excellent research accomplishments, a Program Director (hereinafter referred to as "PD") is assigned to each integrated project, and a Program Supervisor (hereinafter referred to as "PS") and Program Officer(s) (hereinafter referred to as "PO") to each program. In addition, with regard to programs related to the disease areas (cancers, lifestyle-related diseases, mental and neurological disorders, geriatrics and dementia, rare and intractable diseases, growth and infectious diseases etc.) conducted in a cross-cutting manner under the integrated projects, in order to flexibly manage each area Disease Area Coordinators (hereinafter referred to as "DC") are assigned to each area.

The PS and PO have complete knowledge and understanding of the progress status of this program overall and provide the necessary guidance and advice to ensure that this program runs smoothly. Furthermore, research institutions 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 cancelled (including early conclusion of projects due to achievement of R&D plans) as deemed necessary.

In this program, under the PS and PO, an optimal mix of researchers is assembled from industry, academia, and government on a cross-organizational basis, and R&D projects are organized to construct a time-limited system for conducting R&D. The R&D PIs and Co-investigators oversee work in the R&D area with the cooperation of R&D Area Advisers and others to accomplish the R&D objectives designated by the national government (Ministry of Education, Culture, Sports, Science and Technology (MEXT)). Receiving support from the PS and PO in accordance with their management policies, the R&D PIs of AMED-CREST and PRMIE R&D projects interact with R&D Area Advisers and others and facilitate collaboration among participating researchers with the aim of generating innovative seeds. The R&D PIs also actively create and utilize networks through collaborations with entities both in Japan and overseas, and advance the R&D projects they have proposed in accordance with management policies of the PS and PO.

* https://www.kantei.go.jp/jp/singi/kenkouiryou/senryaku/index.html (in Japanese)

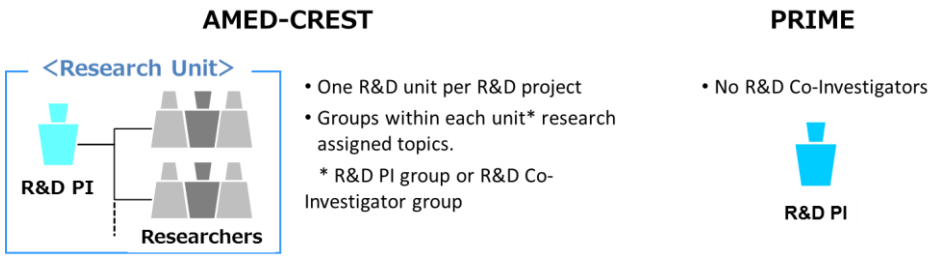
1.2.2 R&D Unit Organization

(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 2.2 for further requirement details.

(B) For PRIME, the R&D PI takes responsibility for implementing their own R&D projects and carrying out R&D that will contribute to the objectives of the overall R&D area 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. 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.



1.2.3 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.

(A) "Principal Institution" refers to the research institution with which the R&D Principal Investigator (PI) is affiliated. It is as a general rule the PI's main place of research,[1] which has concluded a contracted R&D agreement with AMED[2] directly. The Principal Institution should be the research institution, etc. referred to in Chapter 2.

(B) "Subsidiary Institution" refers to a research institution other than the Principal Institution with which a Co-Investigator is affiliated. It is as a general rule the Co-Investigator's main place of research.[1] In the event that a contracted R&D agreement has not been directly concluded with AMED, a subcontracted R&D agreement shall be concluded with the Principal Institution.

(C) "PI" refers to a researcher (one person) who takes responsibility for formulating an R&D implementation plan and compiling the accomplishments for the R&D project for which the application is being submitted during the implementation period. The PI is affiliated with the Principal Institution.

(D) "Co-Investigator" refers to a researcher who shares implementation of R&D items with the PI and takes responsibility for carry out the relevant R&D items. The Co-Investigator is affiliated with either the Principal Institution or Subsidiary Institution.

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

[1] If the affiliated 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 8.

Chapter 2. Application Requirements

2.1 Eligible Applicants

Eligible Applicants for this program shall be researchers (R&D Principal Investigators (PIs)) affiliated with a research institution in Japan that fulfills the conditions shown in (1)–(5) below and that is their main place of research,[1] and who 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.

(1) Eligible Applicants shall be affiliated with a research institution or other organization 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) Public test and research institution run by local government[4]

(C) University as prescribed under the School Education Act (Act No. 26 of 1947) or university affiliated research institution, etc. (including inter-university research institute corporations).

(D) R&D division or research laboratory, etc. of a private enterprise

(E) A general incorporated association, general incorporated foundation, public interest incorporated association, or public interest incorporated foundation whose main activity purpose is research.

(F) An independent administrative agency as prescribed under Article 2 of the Act on General Rules for Incorporated Administrative Agencies (Act No. 103 of 1999; partially amended on June 13, 2014) or local incorporated administrative agency as prescribed under Article 2 of the Local Independent Administrative Agency Act (Act No. 118 of 2003) whose main activity purpose is research.

(G) Collaborative Innovation Partnership (CIP)[5]

(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 test and research institution affiliated with the Cabinet office; a test and research institution, 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 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] Test and research institution, etc., affiliated with a local government.

[5] Collaborative Innovation Partnership (CIP) pursuant to the Act on Collaborative Innovation Partnership (Act No. 81 of 1961)

(2) In the case that the project is selected, the research institution's facilities and equipment can be used for carrying out the project.

(3) In the case that the project is selected, the research institution is able to carry out administrative procedures such as contract procedures.

(4) In the case that the project is selected, the research institution is capable of responsibly handling any intellectual property (IP) rights (including patents and copyright, etc.) and R&D data generated through implementation of this program.

(5) The research institution is capable of continuing to promote R&D even after this program has concluded, and can support other research institutions and researchers in relation to this program.

In only PRIME, if a researcher who is not affiliated with a research institution, etc. or is affiliated with a research institution, etc. outside of Japan is selected as the PI, the researcher may apply for this program if they are able to become affiliated with a research institution in Japan and create a system for conducting research by October 1, 2023. However, in the case that the above conditions are not met by October 1, 2023, as a general rule the decision to adopt the R&D project shall be cancelled. The applicant's employment status may be checked during the selection process.

Furthermore, in order to confirm the research institution'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 the main operations undertaken by the institution and its finances (assets, debts, etc.).

2.2 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 realizing the R&D concepts 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 concepts 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 following the appropriate procedures.

*The participation of overseas research groups is eagerly welcomed in proposals to AMED-CREST. However, with regard to groups affiliated to overseas research institutions, as AMED does not in principle provide research funds securing independent research funding is a requisite condition. In exceptional cases in which a researcher affiliated with an overseas research institution participates in the proposed R&D project as an R&D Co-Investigator, the following conditions must be met.

- The R&D concepts can only be realized with the participation of the overseas research institution (the necessity of the overseas research institution in question may be checked during the course of the selection process). In the event that applicants wish to formulate units including research institutions outside of Japan, it is requested that the reason why R&D Co-Investigators affiliated to research institutions outside of Japan are required is detailed in the R&D Proposal.
- The overseas research institution is required to transfer, free of charge, intellectual property rights to the Principal Institution.
- 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 indirect costs must not exceed 30% of the direct costs.

2.3 Limitations on Duplicate Applications within the Strategic Basic Research Programs (including the Advanced Research and Development Programs for Medical Innovation)

The Advanced Research and Development Programs for Medical Innovation, which solicits R&D proposals through these Application Guidelines, is positioned as part of the Strategic Basic Research Programs, competitive funding programs, under the auspices of the Ministry of Education, Culture, Sports, Science and Technology (MEXT). Accordingly, with regard to AMED-CREST and PRIME R&D proposals for FY2023 under the Advanced Research and Development Programs for Medical Innovation, the following limitations* on duplicate applications have been stipulated in advance in accordance with policies prescribed for the Strategic Basic Research Programs, which are operated by AMED and the Japan Science and Technology Agency (hereinafter referred to as "JST").

* Programs to which limitations on duplicate applications apply are programs in which the implementing institution is either AMED or JST and that are promoting strategic basic research in accordance with R&D objectives and strategic objectives formulated by MEXT under the Strategic Basic Research Programs scheme of MEXT. Such programs aim to not only achieve R&D objectives and strategic objectives, but also promote research by a larger number of outstanding researchers; thus, beginning in FY2020, the scope of application limitations has been unified between AMED and JST.

Within the scope necessary to check the presence/absence of duplicate applications described in this item, certain information related to the screening process may be provided to JST.

(1) From among all the R&D areas or research areas under AMED-CREST, PRIME, CREST*, PRESTO*, and ACT-X* for which project proposals are being solicited in FY2023, each applicant may submit an application for only one R&D or research area. However, as an exceptional measure there are some R&D/research areas in which duplicate applications are possible, so please refer to sections (6) and (7) below.

* Strategic Basic Research Programs (creating new technological seeds) implemented by JST that are positions as part of Strategic Basic Research Programs overseen by MEXT. Under CREST, research teams led by Research Directors implement research projects, while PRESTO and ACT-X are programs under which Individual Researchers implement research projects.

CREST: https://www.jst.go.jp/kisoken/crest/

PRESTO: https://www.jst.go.jp/kisoken/presto/

ACT-X: https://www.jst.go.jp/kisoken/act-x/

(2) If any of the following should apply to you, your proposal shall be rejected.

If you currently hold any of the positions listed below from (a) to (h), you may not apply as the applicant to the AMED-CREST or PRIME programs (excluding when the research period for the relevant research project ends within FY2023, or you are applying to participate in AMED-CREST or PRIME while carrying out an ACT-X project (early conclusion).*

(a) R&D PIs of AMED-CREST under the AMED Advanced Research and Development Programs for Medical Innovation

(b) R&D PIs of PRIME under the AMED Advanced Research and Development Programs for Medical Innovation

(c) R&D PIs of LEAP and FORCE under the AMED Advanced Research and Development Programs for Medical Innovation

(d) Research Directors of CREST under the JST Strategic Basic Research Programs (Creating New Technological Seeds)

(e) Individual Researchers of PRESTO under the JST Strategic Basic Research Programs (Creating New Technological Seeds)

(f) Individual Researchers of ACT-X under the JST Strategic Basic Research Programs (Creating New Technological Seeds)

(g) Research Directors of AIP Acceleration Research under the JST Strategic Basic Research Programs (Creating New Technological Seeds)

(h) Research Directors and Co-Research Directors of ERATO under the JST Strategic Basic Research Programs (Creating New Technological Seeds)

* For detailed information, please contact JST.

(3) Under AMED-CREST, the following limitations are placed on applications submitted by applicants as the Co-investigator or project participant of the proposed R&D project.

(a) For applications in the relevant fiscal year, the R&D PI and Co-investigator on the same team cannot interchange roles and submit multiple applications. This limitation applies regardless of whether the R&D proposals are submitted for the same R&D area or different areas. Moreover, this limitation also applies to Research Directors and Lead Joint Researchers for JST CREST project proposals.

* As a general rule, in cases where the above limitation does not apply due to the partial differences in the team organization, etc. but unreasonable duplication/excessive concentration are deemed to exist, certain measures may be taken as necessary. For details, please refer to "5.4 Elimination of Unreasonable Duplication or Excessive Concentration of Research Funds."

(b) If an applicant who currently holds the position of Co-investigator or project participant for an AMED-CREST, FORCE, or LEAP project or of Lead Joint Researcher, Group Leader, or other Research Participant for a CREST or ERATO project newly applies as a Co-investigator or project participant and is shortlisted in this solicitation as a candidate for selection, 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. For details, please refer to "Table 1. Eligibility for Application to and Participation in the AMED-CREST/PRIME Programs."

(c) If the applicant submits an R&D proposal as the R&D PI or Co-investigator or a project participant, and also submits another R&D proposal as the Co-investigator or a project participant, and both R&D proposals are shortlisted as candidates at the same time, the same adjustments as stated in b. above may be made. The same adjustments may also be made with regard to JST CREST project proposals. For details, please refer to "Table 2. Eligibility for Simultaneous Application to and Participation in the AMED-CREST/PRIME Programs".

(4) In applications from FY2022 onwards, it has become possible to simultaneously perform the role of R&D PI for a PRIME project, and that of Co-investigator for an AMED-CREST, FORCE, or LEAP project, or Lead Joint

Researcher for a CREST project or Group Leader for an ERATO project. In addition, it is now possible to simultaneously perform the role of Individual Researcher for a PRESTO, ACT-X or ACT-X (acceleration phase) project, and that of Co-Investigator for an AMED-CREST, FORCE, or LEAP project, Lead Joint Researcher for a CREST project, or Group Leader for an ERATO project. For details, please refer to "Table 1. Eligibility for Application to and Participation in the AMED-CREST/PRIME Programs" and "Table 2. Eligibility for Simultaneous Application to and Participation in the AMED-CREST/PRIME Programs."

(a) When applying to AMED-CREST, it is possible for an R&D PI for a PRIME project or an Individual Researcher for a PRESTO, ACT-X, or ACT-X (acceleration phase) project to be appointed as a Co-investigator for an AMED-CREST project proposal.

(b) If an applicant who is currently the Co-investigator for an AMED-CREST, FORCE, or LEAP project, Lead Joint Researcher of a CREST project, or Group Leader of an ERATO project newly applies to PRIME and is shortlisted in this solicitation as a candidate for selection, 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. For details, please refer to "Table 1. Eligibility for Application to and Participation in the AMED-CREST/PRIME Programs."

(c) If an applicant applies to PRIME and their PRIME project proposal and an AMED-CREST/CREST project proposal in which they are planning to participate as the Co-investigator or Lead Joint Researcher are both shortlisted as candidates, the same adjustments as stated in (b) above may be made. The same adjustments may also be made with regard to JST PRESTO project proposals. For details, please refer to "Table 2. Eligibility for Simultaneous Application to and Participation in the AMED-CREST/PRIME Programs."

(5) Those who are planning to submit an application for LEAP for FY2023 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.

(6) With regard to the AMED R&D area "Integrated understanding of multi-sensing networks and elucidation of their control mechanisms leading to the innovation of medical technologies," duplicate applications for the JST CREST research area "Research on Multi-sensing Biosystems and Development of Adaptive Technologies" and JST PRESTO research area "Multisensory Integration in Biological Systems" will be permitted as an exceptional measure.

* In the above R&D/research areas only duplicate applications for AMED-CREST and JST CREST, and duplicate applications for PRIME and PRESTO will be allowed. However, applicants are requested to submit R&D proposals to both AMED and JST using the forms respectively stipulated by AMED and JST. If proposals are made using the incorrect forms, they will not be accepted. Furthermore, there will be no simultaneous adoption of proposals in the AMED R&D area and the JST research area.

* In the event that a proposal progresses to the interview selection stage, applicants will be requested to submit to AMED information on the participation in and state of applications of AMED-CREST R&D PI, R&D Co-Investigators, R&D participants and PRIME R&D PI and R&D participants in the four collaborating programs.

(Applicants will be informed of the format for filling in this information when progressing to the interview selection stage.)

(7) With regard to PRIME (solo-type) of the AMED R&D area "Bridging the fundamental mechanism of aging and the effective treatment of age-related disease associated with impaired functional system" duplicate applications for the JST PRESTO research area "Fundamental understanding of age-related organismal transformations" will be permitted as an exceptional measure.

* In the above R&D/research areas only duplicate applications for PRIME and PRESTO will be allowed. However, as material explaining the differences between the PRIME and PRESTO applications, it is necessary to submit the "Additional form for duplicate application (Japanese Only)." The Forms shared by the AMED and JST secretariats as submitted items, and serve as referential materials for the selections made under both programs. The format of the "Additional form for duplicate application" is the same for PRIME and PRESTO, and it is posted on the PRESTO Call for Research Proposals pages[†]. When making a proposal to PRESTO, please submit it via e-Rad in conjunction with your R&D Proposal. (Since the form will be shared with JST and AMED, there is no need to submit it to AMED. Please refer to the PRESTO Call for Research Proposals pages for more details.) In the event that the "Additional form for duplicate application" is not submitted despite a duplicate application being made to PRIME and PRESTO, both PRIME and PRESTO will regard the application as unaccepted.

  Applicants are requested to submit R&D proposals to both AMED and JST using the forms respectively stipulated by AMED and JST. If proposals are made using the incorrect forms, they will not be accepted. In addition, there will be no simultaneous adoption of proposals in the AMED R&D area and the JST research area.

* In the event that a proposal progresses to the interview selection stage, applicants will be requested to submit to AMED information on the participation in and state of applications of AMED-CREST R&D PI, R&D Co-Investigators, R&D participants and PRIME R&D PI and R&D participants in the three collaborating programs. (Applicants will be informed of the format for filling in this information when progressing to the interview selection stage.)

[†] JST "Fundamental understanding of age-related organismal transformations"
https://www.jst.go.jp/kisoken/boshuu/teian/en/top/ryoiki/ryoiki_p09.html

Table 1. Eligibility for Application to and Participation in the AMED-CREST/PRIME Programs

Check the following table if you are currently engaged in research under AMED Advanced Research and Development Programs for Medical Innovation (AMED-CREST, PRIME, FORCE, LEAP) or JST Strategic Basic Research Programs (CREST, PRESTO, ACT-X, AIP Acceleration Research, ERATO), unless the research period for your project ends within FY2023.

Current position in ongoing research project \ Position in research proposal		AMED-CREST (AMED)			PRIME (AMED)
		R&D PI	Co-Investigator	Project participant	R&D PI
AMED-CREST (AMED)	R&D PI	Not eligible	Eligible[1]	Eligible[1]	Not eligible[2]
	Co-Investigator	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1,3]
	Project participant	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1]
PRIME (AMED)	R&D PI	Not eligible[2]	Eligible[1,3]	Eligible[1]	Not eligible
FORCE (AMED)	R&D PI	Not eligible	Eligible[1]	Eligible[1]	Not eligible[2]
	Co-Investigator	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1,3]
	Project participant	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1]
LEAP (AMED)	R&D PI	Not eligible	Eligible[1]	Eligible[1]	Not eligible[2]
	Co-Investigator	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1,3]
	Project participant	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1]
CREST (JST)	Research Director	Not eligible[2]	Eligible[1]	Eligible[1]	Not eligible[2]
	Lead Joint Researcher	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1,3]
	Other Research Participant	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1]
PRESTO (JST)	Individual Researcher	Not eligible[2]	Eligible[1,3]	Eligible[1]	Not eligible[2]
ACT-X (JST)	Individual Researcher	Eligible[4]	Eligible[1,3]	Eligible[1]	Eligible[4]
AIP Acceleration Research (JST)	Research Director	Not eligible[2]	Eligible[1]	Eligible[1]	Not eligible[2]
	Collaborator	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1,3]
	Other Research Participant	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1]
ERATO (JST)	Research Director	Not eligible[2]	Eligible[1]	Eligible[1]	Not eligible[2]
	Co-Research Director	Not eligible[2]	Eligible[1]	Eligible[1]	Not eligible[2]
	Group Leader	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1,3]
	Representative responsible for concluding a contract research agreement	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1]
	Research Participant	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1]

[1] When AMED and JST are selecting research projects, they shall make adjustments such as reducing R&D costs or selecting only one of the applicant's proposed R&D projects, taking into account issues such as excessive concentration and unreasonable duplication as well as the content and scale of the R&D proposals.

[2] Application is only possible if the approval of the Program Supervisor (PS) and AMED/JST has been received in advance. (Notification must be made a minimum of three weeks before the application deadline.)

[3] In applications from FY2022 onwards, it has become possible to simultaneously perform the role of R&D PI for a PRIME project, and that of Co-investigator for an AMED-CREST, FORCE, or LEAP project, or Lead Joint Researcher for a CREST project or Group Leader for an ERATO project. In addition, it has also become possible to simultaneously perform the role of Individual Researcher for a PRESTO, ACT-X or ACT-X (acceleration phase) project, and that of Co-Investigator for an AMED-CREST, FORCE, or LEAP project, Lead Joint Researcher for a CREST project, or Group Leader for an ERATO project.

[4] If the relevant project is adopted, the ACT-X research shall conclude at the end of the fiscal year (early conclusion). When applying, be sure to notify JST.

Table 2. Eligibility for Simultaneous Application to and Participation in the AMED-CREST/PRIME Programs

Check the following table if you are not currently engaged in research under AMED Advanced Research and Development Programs for Medical Innovation (AMED-CREST, PRIME, FORCE, LEAP) or JST Strategic Basic Research Programs (CREST, PRESTO, ACT-X, AIP Acceleration Research, ERATO).

Position in research proposal 1 / Position in research proposal 2		AMED-CREST (AMED)			PRIME (AMED)
		R&D PI	Co-Investigator	Project participant	R&D PI
AMED-CREST (AMED)	R&D PI	Not eligible	Eligible[1]	Eligible[1]	Not eligible
	Co-Investigator	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1,2]
	Project participant	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1]
PRIME (AMED)	R&D PI	Not eligible	Eligible[1,2]	Eligible[1]	Not eligible
LEAP (AMED)	R&D PI	Eligible[3]	Eligible[1]	Eligible[1]	Eligible[3]
	Co-Investigator	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1,2]
	Project participant	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1]
CREST (JST)	Research Director	Not eligible[4]	Eligible[1]	Eligible[1]	Not eligible
	Lead Joint Researcher	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1,2]
	Other Research Participant	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1]
CREST (JST)	Proposal subject to the Feasibility Study of Specific Research Proposal in the previous fiscal year	Not eligible	Eligible[1]	Eligible[1]	Not eligible
PRESTO (JST)	Individual Researcher	Not eligible	Eligible[1,2]	Eligible[1]	Not eligible[4]
PRESTO (JST)	Proposal subject to the Feasibility Study of Specific Research Proposal in the previous fiscal year	Not eligible	Eligible[1,2]	Eligible[1]	Not eligible
ACT-X (JST)	Individual Researcher	Not eligible	Eligible[1,2]	Eligible[1]	Not eligible
ERATO (JST)	Research Director	Eligible[3]	Eligible[1]	Eligible[1]	Eligible[3]
	Co-Research Director	Eligible[3]	Eligible[1]	Eligible[1]	Eligible[3]
	Group Leader	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1,2]
	Research Participant	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1]
	Proposal subject to the Feasibility Study of Specific Research Proposal in the previous fiscal year	Eligible[3]	Eligible[1]	Eligible[1]	Eligible[3]

[1] If both research proposals 1 and 2 are both shortlisted as candidates, AMED and JST shall make adjustments such as reducing R&D costs or selecting only one of the applicant's proposed R&D projects, taking into account issues such as excessive concentration and unreasonable duplication as well as the content and scale of the R&D proposals.

[2] In applications from FY2022 onwards, it has become possible to simultaneously perform the role of R&D PI for a PRIME project, and that of Co-investigator for an AMED-CREST, FORCE, or LEAP project, or Lead Joint Researcher for a CREST project or Group Leader for an ERATO project. In addition, it has also become possible to simultaneously perform the role of Individual Researcher for a PRESTO, ACT-X or ACT-X (acceleration phase) project, and that of Co-Investigator for an AMED-CREST, FORCE, or LEAP project, Lead Joint Researcher for a CREST project, or Group Leader for an ERATO project.

[3] If both research proposals 1 and 2 are both shortlisted as candidates, the relevant applicant must select one of the proposed R&D projects in which to participate.

[4] The following combinations of duplicate applications can be made as exceptional measures: (1) AMED-CREST (unit-type) of the AMED R&D area "Integrated understanding of multi-sensing networks and elucidation of their control mechanisms leading to the innovation of medical technologies" and the JST CREST research area "Research on Multi-sensing Biosystems and Development of Adaptive Technologies"; (2) PRIME (solo-type) of the AMED R&D area "Integrated understanding of multi-sensing networks and elucidation of their control mechanisms leading to the innovation of medical technologies" and the JST PRESTO research area "Multisensory Integration in Biological Systems"; (3) PRIME (solo-type) of the AMED R&D area "Bridging the fundamental mechanism of aging and the effective treatment of age-related disease associated with impaired functional system" and the JST PRESTO research area "Fundamental understanding of age-related organismal transformations." *

However, there will be no simultaneous adoption of proposals in the AMED R&D area and the JST research area. If both research proposals are shortlisted as candidates, it will be up to applicants themselves to coordinate which of the two they will implement. This will mean, for example, withdrawing one of the other proposals made to AMED-CREST and JST CREST or one of the other proposals made to AMED PRIME and JST PRESTO.

* Note that when applying to JST PRESTO, it is necessary to submit the "Additional form for duplicate application (Japanese Only)." (Refer to Chapter 2, 2.3 (7), Chapter 3, 3.2.2, and Chapter 5, 5.1.1 for more details.)

2.4 Relationships between the applicant and the Program Supervisor/ Program Officer

Applicants are eligible for application to this round of solicitation even if they have conflict of interests with the Program Supervisor or Program Officer (This eligibility rule has been in effect since FY 2018 solicitations).

2.5 Important Items Regarding Application

2.5.1 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 institution carrying out the R&D project and AMED. For details, please refer to Chapter 8.

2.5.2 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 programs at individual ministries and agencies (receipt of application => selection => management of selected projects => application to register accomplishments 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 accomplishments your proposed R&D project can produce before completing the proposal documents. For details, please refer to Chapter 5.

* "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.

2.5.3 Security Trade Control (Countermeasures to Technology Leakage Overseas)

At research institutions, 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 institutions 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 (Act 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) (including those falling under the "Specific Categories"*) 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.

*Those falling under the "Specific Categories" refer to residents of Japan under the significant influence of non-residents of Japan, i.e. residents of Japan with close diplomatic or financial links with overseas governments, companies or institutions stipulated in 1.(3) k.(i)–(iii) of the "Notification for Transactions or Acts of Transferring Technology Requiring Permission pursuant to Article 25 (1) of the Foreign Exchange and Foreign Trade Act and Article 17 (2) of the Foreign Exchange Order."

Furthermore, according to the Foreign Exchange Act, in the event that the exporting of List Control goods or provision of List Control technologies overseas is conducted as a business, it is necessary to create a security trade control system.* Therefore, prior to concluding the agreement checks may be made to assess whether this program is intending to export goods or technologies that are subject to the export regulations of the Foreign Exchange Act, and in the event that there is an intention to export these checks may also be conducted on whether or not a control system is in place. In the event that there is an intention to export but no control systems in place, the development of a control system is required by whichever is earliest of the time of export or completion of the program. It should be noted that with regard to the situation surrounding the above checks, in response to requests by the Ministry of Economy, Trade and Industry (METI) a report may be made to the Ministry. In addition, with regard to technologies etc. acquired through the program, in the event that they are judged to be in violation of the Foreign Exchange Act, the agreement may be cancelled in part or in whole.

*Exporters are obliged to strictly observe the "standards to be complied with by exporters, etc." stipulated in Article 55-10 (1) of the Foreign Exchange Act. In addition, the "security trade control system" herein is based on a control system compliant with the "standards to be complied with by exporters, etc.," and is an organizational internal control system that prevents illicit exports before they happen by the appropriate handling of list control goods exports and list control technologies provision to overseas countries.

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

- Ministry of Economy, Trade and Industry: Security Trade Control (general)
  https://www.meti.go.jp/policy/anpo/ (in Japanese)
  (Q&A: https://www.meti.go.jp/policy/anpo/qanda.html) (in Japanese)
- Center for Information on Security Trade Control
  https://www.cistec.or.jp/ (in Japanese)
- Guidance for Management of Sensible Nuclear Technology (SNT) in Relation to Security Trade Control (for universities/research institutions)
  https://www.meti.go.jp/policy/anpo/law_document/tutatu/t07sonota/t07sonota_jishukanri03.pdf (in Japanese)
- Security Trade Control Regulations Manual for universities and research institutions
  https://www.meti.go.jp/policy/anpo/daigaku/manual.pdf (in Japanese)
- Center for Information on Security Trade Control Model CP (for corporations)
  https://www.cistec.or.jp/export/jisyukanri/modelcp/modelcp.html (in Japanese)
- Security Export Guidance (introduction)
  https://www.meti.go.jp/policy/anpo/guidance.html

2.5.4 Stringent Implementation of United Nations Security Council Resolution 2321

In response to North Korea's nuclear test of September 2016 and its repeated ballistic missile launches, on November 30, 2016 (local time in New York) the United Nations Security Council (hereinafter referred to as "the UN Security Council") adopted Resolution 2321, substantially adding and bolstering sanction measures against North Korea. With regard to this, on February 17, 2017 the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) issued to all relevant organizations its Directive Regarding the Stringent Implementation of United Nations Security Council Resolution 2321 (MEXT No.98 of FY2017).

Paragraph 11 of the Resolution suspended not only scientific and technical cooperation regulated by the Foreign Exchange and Trade Act but also all cooperation other than for the purpose of medical exchanges. It is vital that research institutions take care to stringently implement the Resolution in the course of all research activities including the relevant contracted research.

Please see below for the United Nations Security Council Resolution 2321.

- United Nations Security Council Resolution 2321 (2016)
  https://www.undocs.org/S/RES/2321(2016)

2.5.5 Enthusiastic Participation and Action of Young Researchers

In line with the common intent of programs funded by public research funding AMED broadly promotes the nurturing and fostering of researchers who will shoulder the future of Japan and who through which R&D accomplishments will be put to use for the good of society. Subsequently, it is desirable that enthusiastic efforts are made to assign young researchers in AMED programs.

Young researchers in the AMED programs are defined as those males who are under 40 years old as of April 1, 2023 (i.e. who were born on or after April 2, 1983); females who are under 43 years old as of April 1, 2023 (i.e. who

were born on or after April 2, 1980); or those who acquired their doctorate less than 10 years ago. However, for those who have taken pre- or post-natal leave or child-rearing leave, the age restriction (under 40 years old for males and 43 years old for females) may be extended by the number of days they took the leave.

2.5.6 Data Sharing

With regard to the treatment of data arising from the accomplishments of R&D in the medical field, the importance of data sharing between researchers is recognized as the data is also useful to researchers sharing the same awareness of problems. At the same time, in the case of data arising from R&D implemented through public funding, because of its highly public nature and considerable public benefit moves are afoot to attempt to expand the possibility of their secondary use through registration with repositories and timely release. Moreover, in order to aim for the practical application of R&D there is a need to share detailed and accurate clinical information and genome information among not only academic research bodies such as universities and research institutions but also the industrial sector, including private corporations that will make industrial use of such data, to cooperate and develop new diagnostic and treatment methods.

At AMED, whenever contracted R&D agreements are concluded the submission of a data management plan (hereinafter referred to as “DMP”) by research institutions is made obligatory. In addition, the AMED Basic Policy on Handling of R&D Data that compiles the definition of R&D data and policy regarding the treatment etc. of R&D data, and the Guidelines on AMED Research Data Utilization* that compiles the specific management guidelines have been formulated, and are available on the AMED website. For the details regarding submission of DMPs, please refer to Chapter 7.

Furthermore, the contracted R&D agreements with AMED in principle prohibit the research institutions, etc. from disclosing or providing to third parties any type of R&D data generated, acquired or collected in connection with R&D supported (contracted or assisted) by AMED. However, in cases in which it is permitted according to the AMED guidelines mentioned above, or when the prior consent of AMED has been obtained, it is possible to disclose or provide data to third parties.

In addition, R&D data is categorized into the four types of “unrestricted openly shared data,” “restricted openly shared data,” “restricted closed shared data,” and “unshared data,” while data other than data that it would be inappropriate to divulge to third parties is in principle designated as either unrestricted openly shared data or restricted openly shared data, and is required to be published. Furthermore, even if certain data falls under the categories of either unrestricted openly shared data or restricted openly shared data it is permitted to share it only with specific third parties for the duration of the period when it is treated as restricted closed shared data prior to release. For further details please refer to the Guidelines on AMED Research Data Utilization. *

*https://www.amed.go.jp/koubo/datamanagement.html (in Japanese)

In order to promote the utilization of the data obtained from R&D supported by AMED, we are pursuing the creation of the AMED Data Utilization Platform (hereinafter “the platform”).

*https://www.kantei.go.jp/jp/singi/kenkouiryou/data_rikatsuyou/dai2/siryou2.pdf (in Japanese)

With regards to the human whole genome sequence (WGS) data shared by the platform, which serves as an access point, with the objectives of equally assuring the quality of data already planned for sharing over the platform, and ensuring they are easily usable in joint international research projects with other countries involved in advanced genome analysis, it is necessary that the sequence data is created using the same analysis protocol as in the data already planned for sharing over the platform.

Therefore, in the case that human WGS analysis[1] is included in R&D plans, it is necessary to submit information on the protocol used in the analysis.[2]

With regards to the human WGS analysis protocol, it is particularly necessary to stipulate the following items:

- Library construction (kit name, fragment length etc.)
- Sequencing reaction (kit name, read length etc.)
- Name of sequence analyzer (name of analyzer, serial number etc. Name of subcontractor if to be outsourced)
- Quality control (QC) method
- Methods of mapping to the reference genome and assembly

In addition, with regard to the human WGS analyses conducted under AMED R&D, regardless of whether or not the analysis is outsourced to an external organization etc., the samples used in the genome sequence analyses and the results of the genome sequence analyses (including FASTQ raw sequence data and data generated in the process leading up to obtaining VCF data) may not be taken outside of Japan except in the following cases:[2]

- The publishing in academic journals or presentation at academic meetings of the results of human WGS analyses or the knowledge obtained from the observation of them.
- In cases in which researchers believe there are reasonable grounds for joint international research or use by corporations etc., discuss them on an individual basis with AMED, and AMED subsequently confers with the relevant ministries and agencies and obtains their exceptional consent.

It should be noted that when data management plans are reviewed or revised pursuant to the Guidelines on AMED Research Data Utilization and the contracted R&D agreement,* it is necessary to receive the approval of AMED.

*https://www.amed.go.jp/content/000079403.pdf (in Japanese)

[1] Whole genome sequence (WGS) analysis

- Here this refers to WGS and whole exome analysis using next-generation sequencers. Please note that it does not target some specific genome analyses such as epigenome, ChIP-seq, and RNA-seq, even if next-generation sequencers, various array and the Sanger-sequence method are used.
- This means the process leading up to obtaining VCF data from biological samples.

[2] The treatment of human WGS analysis in the Ministry of Health, Labour and Welfare's REpository of Data and Biospecimen of INfectious Disease (REBIND), will be pursuant to the guidelines of REBIND.

Reference: Data Sharing Policy for the Realization of Genomic Medicine
https://www.amed.go.jp/koubo/datasharing.html (in Japanese)

Chapter 3. 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 1; for application/selection implementation methods, please refer to Chapter 4.

3.1 Scale of R&D funds, R&D period, Planned Number of Awarded Projects, etc

#	R&D Projects Being Solicited		Scale of R&D funds (excluding indirect costs[1])	Period in which R&D is Scheduled to be Implemented	Planned Number of New Awarded Projects
1	Elucidation of mechanisms for stress responses to disease development (PS: Hiroyasu Iso) (PO: Hidenori Ichijo) (PO: Tsuyoshi Sekitani)	AMED-CREST (Unit-type)	Max. of 300 million yen for total R&D period for each project	Max. of 5.5 years FY2023–FY2028	Around 4–6 projects
		PRIME (Solo-type)	Max. of 40 million yen for total R&D period for each project	Max. of 3.5 years FY2023–FY2026	Around 8–12 projects
2	Bridging the fundamental mechanism of aging and the effective treatment of age-related disease associated with impaired functional system (PS: Naoki Mochizuki) (PO: Akiyoshi Fukamizu) (PO: Koji Yasutomo)	AMED-CREST (Unit-type)	Max. of 250 million yen for total R&D period for each project	Max. of 5.5 years FY2023–FY2028	Around 4–6 projects
		PRIME (Solo-type)	Max. of 40 million yen for total R&D period for each project	Max. of 3.5 years FY2023–FY2026	Around 8–12 projects
3	Immunological memory: Understanding, regulation and medical innovation[2] (PS: Toshinori Nakayama) (PO: Kiyoshi Takeda)	AMED-CREST (Unit-type)	Max. of 300 million yen for total R&D period for each project	Max. of 5.5 years FY2023–FY2028	Around 3–5 projects
4	Integrated understanding of multi-sensing networks and elucidation of their control mechanisms leading to the innovation of medical technologies[3] (PS: Ryozo Nagai) (PO: Shoji Takeuchi) (PO: Kohji Nishida)	AMED-CREST (Unit-type)	Max. of 300 million yen for total R&D period for each project	Max. of 5.5 years FY2023–FY2028	Around 2–4 projects
		PRIME (Solo-type)	Max. of 40 million yen for total R&D period for each project	Max. of 3.5 years FY2023–FY2026	Around 8–12 projects
5	Generating research infrastructure and novel technologies for anti-infective drug and vaccine discovery[2,3] (PS: Yohei Doi) (PO: Yoshiharu Matsuura)	AMED-CREST (Unit-type)	Max. of 300 million yen for total R&D period for each project	Max. of 5.5 years FY2023–FY2028	Around 2–4 projects

Note 1. “Scale of R&D Funds” is an approximate estimate guide.

Note 2. “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.

[1] Indirect costs are 30% of R&D costs (direct costs).

[2] Calls for proposals only for Unit-type (AMED-CREST) projects will be made in this R&D area.

[3] The 2023 solicitation will be the final call for proposals.

3.2 Outline of R&D Projects for Which Applications Are Being Solicited

3.2.1 Elucidation of mechanisms for stress responses to disease development

Program Supervisor (PS): Hiroyasu Iso, Director of Institute for Global Health Policy Research (iGHP), Bureau of International Health Cooperation, National Center for Global Health and Medicine

Program Officer (PO): Hidenori Ichijo, Professor, Graduate School of Pharmaceutical Sciences/ Laboratory of Cell Signaling, the University of Tokyo

Program Officer (PO): Tsuyoshi Sekitani, Professor, The Institute of Scientific and Industrial Research, Osaka University

* R&D Area for the Research and Development Objective “Elucidation of mechanisms for stress responses to disease development” (page 104)

Outline of the Research and Development Area

We are surrounded by various different stressors, including physical, chemical, biological, and emotional or psychological stimuli. New stressors have also emerged because of the changes in our lifestyles and social environments during the recent COVID-19 pandemic. Prevention of diseases triggered by such stressors is important to improve our QOL. However, it is difficult to get an objective and accurate understanding of the biological responses to various stressors, and we still do not have a clear view of what type of exposure to stress can cause homeostatic breakdown in the individual that leads to pathogenesis in which many unknown mechanisms involved. We therefore need to identify at the early stages the biological danger signals that occur in response to stress exposure and prevent disease before it occurs.

Research into stress conducted in Japan has tended to involve extensive research at the molecular and cellular levels, rather than research in humans at the individual level. Research at the molecular and cellular level is important for a reductive understanding of the elements involved in disease onset mechanisms, but it is vital to conduct research in individuals if we are to develop a scientific understanding of the diversity and complexity of the body’s response to various stressors we are exposed to. If we are to utilize R&D into stress for preventive medicine in the future, we must combine molecular/cellular level research with individual level research and develop an understanding of stress responses at the individual level. We also think that the foundations are being laid for the development of technologies to allow accurate and long-term measurement of changes in biological information due to stress, now that measuring devices are becoming more sophisticated (highly accurate, rapid, compact, or wearable devices etc.), communications technologies are handling greater volumes of data at higher speeds, and artificial intelligence is becoming utilized more conveniently.

In this research and development area, the goal is to develop a scientific understanding of stress responses at the individual level and the mechanisms leading to disease onset. The research will include integrated analyses of phenomena and the molecular/cellular level at the individual level in response to stress and will be performed through a close collaboration between researchers engaged in basic life science fields and clinical medicine, as well as with

researchers in other disciplines including epidemiology, measurement engineering, or computer sciences. Having developed this understanding, further goals are the discovery and development of drugs that target stress, as well as the identification of new stress markers that provide objective indicators of biological responses to stress exposure and the development of new measuring devices or signal processing technologies that allow accurate, detailed, and long-term capture of biological information that fluctuates subtly in response to stress.

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

Under this R&D area, the goal is to scientifically elucidate the biological responses at various different levels, from molecular/cellular levels to individual levels, caused by physical, chemical, biological, or emotional/psychological stress, and to develop an integrated understanding of stress responses and the mechanisms involved from the molecular/cellular level to the individual level. Further goals include research into the identification of new stress markers that provide objective indicators of stress status in humans and the development of new measuring devices or signal processing technologies that allow accurate, detailed, and long-term capture of the subtle changes in biological information caused by stress exposure. Specific goals include (1) elucidation of stress adaptation or avoidance systems in humans with a focus on applications in disease prevention, and elucidation of the mechanisms involved between the breakdown of these systems and disease onset; (2) identification of markers that allow objective evaluation of stress status in humans or prediction of disease onset due to stress, and elucidation of their pathophysiological significance; and (3) research and development of new techniques or methods, new measuring devices, or signal processing technologies that allow accurate, detailed, and long-term capture of human biological information that fluctuates subtly with exposure to stress.

(1) AMED-CREST (unit-type)

Under AMED-CREST, we invite proposals for research that will involve the formation of an R&D unit to facilitate close collaboration between researchers in basic life science research fields and in clinical medicine, as well as with researchers in other disciplines including epidemiology, measurement engineering, or computer sciences, with the goal of combining research at the molecular/cellular level with the individual level and developing an understanding and establishing objective evaluation methods for the human body's response to stress. The stressors present in our living environments are complex and diverse and are present for our entire life, and the responses of our bodies to these stressors are accordingly complex and diverse. To develop a scientific understanding of these factors, we look for participation by researchers in a wide range of fields beyond conventional life science research frameworks, such as AI researchers or data scientists.

We expect basic researchers to take the findings from R&D at the molecular or cellular level and to collaborate with clinical medicine researchers to investigate and develop an understanding at the individual level in humans. We look for epidemiologists to work with basic researchers on stress markers or mechanisms as predicted from cohort research and other types of investigations in order to investigate and develop an understanding at the molecular or cellular level, or to work with clinical medicine researchers to investigate and develop an understanding at the individual level in humans. For measurement engineering or computer science researchers, we look for the invention

of technologies needed by basic researchers in the life sciences, clinical medicine researchers, or epidemiology researchers to allow the establishment of technologies to objectively evaluate stress.

Below we provide examples of anticipated R&D proposals in this R&D area, but we are looking for innovative research proposals that go beyond these examples.

- Research to clarify the sensitivity, vulnerability, tolerance, and resilience to stress of healthy individuals and to understand individual differences in these responses, based on defined molecular entities, or to elucidate molecular entities using robust methodologies, with the goal of understanding normal biological responses to stress
- Research to develop methodologies to objectively assess at the individual level the biological responses to stress, understanding quantitative factors over time in physiological or pathophysiological changes due to stress (e.g., qualitative or quantitative changes in biological factors)
- Research to elucidate stress level thresholds relevant to disease onset (including acute, chronic, or cumulative perspectives)
- Investigations at the individual level to explore new stress markers for objective evaluation of stress status in humans, elucidate their pathophysiological significance, and determine whether these markers are objective indicators
- Research and development of new measurement methods, new optical devices, or non-invasive wearable devices to measure changes in stress markers, such as physicochemical factors on the body surface or biological factors in sweat, blood, or urine that are triggered by stress
- Research to elucidate the complex and multidimensional biological responses triggered at various life stages by the build-up or sum total of the various types of stress we are exposed to in our daily living environments (including use of data technologies or AI)
- Data-driven research through existing or new cohort research or using biobanks in order to identify stress markers
- New cohort research aimed at exploring new stress markers and investigating their utility

Under AMED-CREST, our focus is on understanding stress responses at the individual level and evaluation of stress levels, so we will give precedence to the following selection criteria:

(A) Research involving the formation of an R&D unit, with close collaboration between researchers in basic life science research fields and in clinical medicine, as well as with researchers in other disciplines including epidemiology, measurement engineering, or computer sciences.

(B) Research plans that include work in individual humans or animals. However, research plans that only include work in individual animals need to include a reasonable explanation of how this links to research at the individual human level.

(C) Research proposals at the molecular or cellular level that do not include plans for research at the individual level need to include a reasonable explanation of how this links to research to promote health or prevent disease in humans.

Where the proposals include research using human samples, ideally, ethical approval for the use of human samples will have already been given at the time of application, but if more time is needed for approval, please ensure that the plan includes details on how ethical approval will be obtained and the number of samples to be analyzed, etc. If the proposal is selected, please implement the next steps to apply for and obtain ethical approval without delay.

○ We will select approximately 4 to 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 R&D period.

(2) PRIME (solo-type)

The PRIME program involves research performed by an individual researcher in his or her specialist field. We invite proposals for highly innovative research in the R&D areas as described in the AMED-CREST program, particularly for the items described below. We also are calling for challenging research proposals not limited to these items.

- Elucidation of molecular and cellular mechanisms of stress responses using model cells or model animals
- Early-stage research and development aimed at exploring and identifying new stress markers
- Elucidation of the mechanisms of responses to stress using human samples
- Challenging research and development aimed at measuring biological information that fluctuates according to exposure to various types of stress

Because this area is aimed at understanding stress responses at the individual level in humans, for PRIME research as well, we welcome proposals in the life sciences that can connect in the future to medical sciences and healthcare. However, for engineering proposals, there is no need to provide at the proposal stage the specific details of how the research connects to the medical sciences and healthcare. We look for proposals for unique measurement methods or devices based on new perspectives. Note that, after selection as the research progresses, we will support collaborations with other researchers in basic life science fields and clinical medicine, as well as in epidemiology, measurement engineering, or computer science.

Given that this program is designed for proposals from individual researchers, we expect to receive proposals from younger researchers. We also look for innovative proposals looking into new concepts or analytical methods in this research area even from researchers not currently engaged in research into stress.

○ We will select approximately 8 to 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 R&D period.

Briefing of solicitation

Please check the following site for more information on the briefing of solicitation (NOTE: Briefing will be only in Japanese.).

https://www.amed.go.jp/en/news/program/1602B_00022.html

3.2.2 Bridging the fundamental mechanism of aging and the effective treatment of age-related disease associated with impaired functional system

Program Supervisor (PS): Naoki Mochizuki, Director General, National Cerebral and Cardiovascular Center Research Institute

Program Officer (PO): Akiyoshi Fukamizu, Director, Life Science Center for Survival Dynamics, Tsukuba Advanced Research Alliance (TARA), University of Tsukuba

Program Officer (PO): Koji Yasutomo, Professor. Graduate School of Biomedical Sciences, Tokushima University

* R&D Area for the Research and Development Objective "Elucidation of the mechanisms relating to changes in biological robustness associated with aging and control of age-related diseases" (page 109)

Outline of the Research and Development Area

The aim of this R&D area is to elucidate the mechanisms relating to changes in biological robustness associated with aging and control of age-related diseases.

Japan's population has aged faster than any other country in the world and is now considered a "super-aged society." Japan faces the urgent challenge of how to extend healthy life years, as well as issues such as rising healthcare expenditure due to the widening gap between average life expectancies and healthy life expectancies. There has been a sharp increase in aging and longevity research over the past few years in various countries around the world, investigating how to delay or prevent aging and how to improve pathophysiology. In Japan as well, research thus far has included basic research to understand the aging phenomenon using molecular biology and other approaches, as well as research looking at the control of age-related diseases by clarifying actual pathophysiology and investigating prevention, diagnosis, and treatment. As a result, we are gradually developing a deeper understanding of aging mechanisms in the body through research into the removal of senescent cells, the involvement of the CNS network and matters related to various bodily organs.

In this research area, the results from previous research into aging mechanisms etc. will be further developed and aging research will be pursued to explore the fundamental principles of the biological phenomenon of aging in animals and investigate aging mechanisms and disease pathologies in order to contribute to the clarification of new mechanisms to control age-related diseases/pathologies and to accelerate programs aimed at extending healthy life years. To achieve this, the Japan Agency for Medical Research and Development (AMED) and Japan Science and Technology Agency (JST) will initiate three programs simultaneously (PRESTO, AMED-CREST, and PRIME) and will work in partnership on the research.

At AMED, model organisms will be used to discover the causes of aging from genetic, biological and physical (environmental) perspectives through the understanding of how multi-dimensional aging-related changes affect molecules/cells (populations), organs, and the entire body; research will aim to thereby elucidate diverse and complex linking mechanisms and age-related disease mechanisms based on an understanding of aging over time, and develop mechanisms to control aging. The programs will promote research that contributes to an understanding of pathophysiology through new concepts and ideas, based on the principles of and mechanisms involved in aging-

related changes in the body's robustness and resilience. This research is expected to lead to aging indicators based on an integrated understanding of aging control mechanisms; the discovery of factors involved in aging control; the creation of new innovations; the prevention of age-related diseases; and breakthroughs in treatments, with the goal of generating innovations that will help achieve a healthy and long-lived society where people can lead active lives.

At JST, programs will promote research that utilizes the latest technologies and investigates changes during aging with a focus on clarifying the principles of the diverse biological phenomenon involved in the biology of aging, and the basic principles and mechanisms that determine aging and life spans using existing and new model organisms.

AMED and JST will operate an integrated program in this research area, working in partnership on the research pursued by each organization. By combining technologies and diverse findings in different fields and bringing together the research themes pursued by each organization, the two organizations will deepen our integrated understanding of aging research and address world-leading innovative R&D. The organizations will consider the possibility of working together with the Moonshot Research & Development Program (FY2020–29) and its Goal #7 "Realization of sustainable care systems to overcome major diseases by 2040, for enjoying one's life with relief and release from health concerns until 100 years old."

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

This R&D area aims to clarify the biology of the basic mechanisms involved in aging and to develop medical approaches mediated via these mechanisms.

The programs will include research that uses the most up-to-date analytical technologies (genetic, imaging, omics analysis) and can be progressed from analysis in model organisms through to applied research, in order to get close to the essence of how aging causes dysfunction and breakdown in molecules, cells, tissues, organs, and the entire body.

What we recognize as being "aging" is the entire integrated progress in which dysfunction in one part of the body induces a breakdown of all bodily functions.

Rather than research that simply clarifies the cause of dysfunction or the pathophysiology of an age-related disease in a single organ, we think it is more important to investigate the essence of aging and thereby elucidate the fundamental breakdowns in mechanisms and changes due to aging that result in disease onset. We therefore invite research proposals that will help provide an integrated understanding of pathophysiology based on new concepts and ideas that will contribute to the prevention and treatment of disease. In this R&D area, we aim to promote mutual technological guidance, experimental materials exchange, or information sharing between researchers to create a lively area that fosters joint research.

Furthermore, in terms of implementation systems in this R&D area, the plan is for the research to be implemented under the strategic objective "Elucidation of the mechanisms relating to changes in biological robustness associated with aging and control of age-related diseases" decided simultaneously by MEXT, and pursued in partnership with research at JST. We look for researchers in the three programs at AMED and JST to work together in a coordinated fashion, utilizing innovative ideas from young researchers and promoting further development of research.

* Handling of R&D Proposals in this R&D area

In this R&D area, R&D Proposals submitted to AMED may be shared with JST, so all applicants responding to this Call for Proposals are assumed to consent to this sharing of submissions.

(1) AMED-CREST (unit-type)

For this R&D area, we invite proposals for research that will utilize various model organisms and human specimens to explore aging-relevant signaling molecules, factors involved in aging progression and suppression, and aging indicators, and research that is aimed at providing a fundamental understanding of aging in the genome/epigenome, cell, organ status, morphology, function, and entire body phenotype. Specifically, we expect innovative research proposals that provide original perspectives and combine research in different fields in order to elucidate various mechanisms, including control mechanisms relevant to the principles of aging over time and mechanisms that contribute to the onset, prevention, and treatment of age-related disease based on the body's mechanisms for robustness and resilience.

We welcome R&D proposals that include the use of imaging and other advanced measuring technologies, database-driven omics analysis, and bioresources to develop and accelerate an integrated understanding of aging research in a wide range of fields. Ideally, the proposals will include the formation of research units comprised of partnerships with research institutions or pharmaceutical companies in Japan and overseas, and combine various different research fields, such as molecular biology, biochemistry, cell biology, neuroscience, immunology, regenerative medicine, clinical medicine, information science, system biology, or synthetic biology.

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

- Exploration of signaling molecules involved in aging, including nutrition/metabolism immunity/inflammation, biological clocks, stem cells, autophagy, apoptosis, cell competition, mitochondria, and genetic information, and clarification of the control mechanisms for aging progression and suppression that change over time
- Understanding network mechanisms that involve molecules/cells (populations), organs, and the entire body and clarifying mechanisms of action involved in disease
- Identification of anti-aging molecules and substances that act on factors involved in the suppression/control of aging, and clarification of their mechanisms of action
- Clarification of how aging control mechanisms are involved in the body's robustness and resilience to aging that play a role in age-related disease and pathology
- Clarification of the mechanisms involved in aging in age-related diseases (e.g., sarcopenia and frailty) and pathophysiologies (e.g., vascular disease, neurological disorders, metabolic abnormalities, lipid abnormalities)
- Understanding of aging over time, development of new innovations based on pathophysiology mechanisms, exploration of aging biomarkers, and clarification of mechanisms that contribute to disease prevention and treatment

○ We will select approximately 4–6 proposals for AMED-CREST this fiscal year, with a total budget of up to 250 million yen per project for R&D costs (direct costs) over the R&D period.

(2) PRIME (solo-type)

The PRIME program involves research performed by an individual researcher in their specialist field. 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 and innovative programs that could lead to new breakthroughs through research to clarify at the molecular level the mechanisms involved in aging progression and suppression of aging by the body, and research that may lead to healthcare applications. We also invite proposals on the development of novel platform technologies to detect and control aging. During the research implementation phase, rather than focusing only on the proposer's specialist field, we recommend they form networks through active collaboration with other research groups in the same or different fields, particularly AMED-CREST research units and researchers in the JST PRESTO research area "Fundamental understanding of age-related organismal transformations", with a view to future development of this research.

Given that this program is designed for proposals from individual researchers, we will give precedence in selection to proposals from younger researchers who may have innovative new research proposals but often cannot undertake challenging research because of a lack of funds and staff. We are particularly interested in how far the researchers submitting proposals can progress and expand the research in the future in the area of aging research and other research areas. We hope to receive proposals from researchers not currently involved in aging research on ideas for analytical methodologies or new concepts that fit the aims of this research area.

○ 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 R&D period.

○ For this PRIME (solo type) R&D area, duplicate submissions to the JST PRESTO research area "Fundamental understanding of age-related organismal transformations" also initiated under this same R&D Objective will be allowed as an exceptional measure.

However, as material explaining the differences between the PRIME and PRESTO applications, it is necessary to submit the "Additional form for duplicate application (Japanese Only)." The Forms shared by the AMED and JST secretariats as submitted items, and serve as referential materials for the selections made under both programs. The format of the "Additional form for duplicate application" is the same for PRIME and PRESTO, and it is posted on the PRESTO Call for Research Proposals pages. When making a proposal to PRESTO, please submit it via e-Rad in conjunction with your R&D Proposal. (Since the form will be shared with JST and AMED, there is no need to submit it to AMED. Please refer to the PRESTO Call for Research Proposals pages for more details.) In the event that the "Additional form for duplicate application" is not submitted despite a duplicate application being made to PRIME and PRESTO, both PRIME and PRESTO will regard the application as unaccepted.

Applicants are requested to submit R&D proposals to both AMED and JST using the forms respectively stipulated by AMED and JST. If proposals are made using the incorrect forms, they will not be accepted. In addition, there will be no simultaneous adoption of proposals in the AMED R&D area and the JST research area.

Briefing of solicitation

Please check the following site for more information on the briefing of solicitation (NOTE: Briefing will be only in Japanese.).

https://www.amed.go.jp/en/news/program/1602B_00022.html

JST “Fundamental understanding of age-related organismal transformations”

https://www.jst.go.jp/kisoken/boshuu/teian/en/top/ryoiki/ryoiki_p09.html

3.2.3 Immunological memory: Understanding, regulation and medical innovation

Program Supervisor (PS): Toshinori Nakayama, President, Chiba University

Program Officer (PO): Kiyoshi Takeda, Professor, Graduate School of Medicine, Osaka University

* R&D Area for the Research and Development Objective “Immunological memory: Understanding, regulation and medical innovation” (page 114)

Outline of the Research and Development Area

Immunological memory is an important host defense system that functions against infectious microorganisms, but is also closely implicated in the pathogenesis of various diseases, including cancer and allergy/autoimmune disease. Immunological memory is a potential target for the development of clinical methods to predict, prevent, and treat such diseases, so a better understanding of the mechanisms will be vital to lay the foundations for medical advances in the management of these diseases. Creation of new concepts of immunological memory will be expected by investigating the mechanism on the establishment of memory based on recognition of self and non-self, memory against pathogenic and symbiotic microorganisms, and pathogenic memory vs. beneficial memory.

Basic research on immunology to date has mostly been performed using mice and has focused on investigating short-term immune responses. The difference in the immune system between humans and animal models such as mice has been a barrier to the application of basic research achievements to the clinical setting. However, the importance of the understanding of the human immune system is rapidly becoming clear as a countermeasure against the COVID-19 pandemic, and basic research to understand human immunological memory is now seen as even more important. A better understanding of how immunological memory in humans is formed and maintained, how it is activated according to the environmental situation, and how it becomes weaker and disappears, will help us to develop new perspectives on the management of the numerous diseases in which the immune system is closely involved.

The goal of this R&D area is to create medical innovations that will contribute to predicting and regulating diseases like cancer, infectious disease, and allergy/autoimmune disease, through a hierarchical and multifaceted understanding of immunological memory in humans by applying advanced research technologies such as the recently developed single-cell/repertoire analyses and structural analyses using cryo-electron microscopy.

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

This R&D area aims to clarify the mechanism of immunological memory in humans, to integratively understand the immunological memory that are closely involved in the onset, exacerbation, and remission of the diseases described above by using the latest, most-advanced research technologies, and to create medical innovations to predict and control these diseases. In particular, we welcome R&D proposals that will contribute to: (1) a new and fundamental understanding of how human immunological memory is formed, maintained, and lost; (2) clarification of novel mechanisms of cancer immunity mediated by human immunological memory; (3) an understanding of human immunological memory against infectious diseases in societies living with COVID-19 and after the COVID-19

pandemic; and (4) development of novel methods controlling allergic and autoimmune diseases, based on an understanding of human immunological memory.

AMED-CREST (unit-type)

Research on human immunological memory is a field that is becoming increasingly competitive around the world. To discover novel medical innovations or scientific concepts, it is necessary to involve collaborations not only between immunologists and clinical researchers, but also with researchers in other fields (e.g., bioinformatics, structural biology, metabolomics, mathematical modelling, chemical biology, imaging, or microbiology) who possess original analytical technologies or cutting-edge methods. We look forward to applications by powerful and very active research teams who will be able to lead immunological memory research in global levels over the next 10–15 years.

We have specified cancer, infectious disease, and allergic and autoimmune diseases as the targets, but immunological memory is deeply involved in other diseases as well, so we also look forward to R&D plans aiming the elucidation of mechanisms that point to new concepts for the onset, prevention, and regulation of those diseases.

We show examples of R&D proposals below. However, we also welcome proposals on other types of R&D based on unique hypotheses.

- Comprehensive understanding of the mechanisms underlying the establishment of memory in lymphocytes and innate immune cells, and the regulatory mechanisms of immunological memory by Treg cells, tissue-resident immune cells, and even non-immune cells
- Development of animal models or analytical technologies that contribute to our understanding of human immunological memory
- Changes in immunological memory over the course of life and clarification of their regulatory mechanisms
- Understanding of the impact of environmental factors including microbiota on immunological memory
- Clarification of the mechanisms how memory is established and regulated in the mucosal immune system
- Clarification of novel mechanisms of cancer immunity from the perspective of immunological memory
- Clarification of mechanisms how genetically engineered immune cells control immunological memory by in ex-vivo gene therapy
- Understanding of immunological memory against various pathogens
- Clarification of mechanisms for immune activation and immune escape based on an understanding of immunological memory in emerging and re-emerging infectious diseases
- Development of innovations for new diagnostic, preventive, and therapeutic methods by the latest wet and dry research approaches, based on immunological memory with a particular focus on personalized medicine for infectious diseases
- Identification of pathogenic memory cells in allergic and autoimmune diseases, and clarification of functional role of those cells in the pathogenesis of these diseases
- Development of innovations for new therapeutic methods for allergic and autoimmune diseases through the elimination of immunological memory
- Clarification of the mechanisms by which immunological memory is involved in the pathogenesis of cardiovascular, metabolic, and neurological diseases, etc

- Clarification of the mechanisms by which immunological memory is involved in chronic rejection reactions following organ transplantation

Research to understand human immunological memory will progress effectively if performed with a correct understanding of the similarities and differences between mouse and human immune systems and pursued through an efficient interaction between mouse and human researches. We strongly recommend that your proposal not be restricted to investigations in animal models, but should involve close collaboration with clinical researchers with expertise in human diseases. At least, your proposal needs to include plans for proof of concept (POC) research in humans/patients, to verify the findings obtained from experiments in mouse and other animal models. The goal is to create new concepts in immunological memory, and to use these concepts as the basis for innovation to develop futuristic preventive and therapeutic methods. We expect to see the research teams that mainly comprise young and mid-career researchers from not only immunology but also various research fields.

In this R&D area, we will collaborate actively with AMED's Strategic Center of Biomedical Advanced Vaccine Research and Development for Preparedness and Response (SCARDA). We encourage the participation of new researchers and the dissemination of research results through collaboration with the Japanese Society for Immunology (JSI) and other relevant academic societies. We will plan to promote immunological memory research in Japan to be world-wide through the use of international platforms that allow interactions with overseas researchers (e.g., the United States-Japan Cooperative Medical Sciences Program and the International Immunological Memory and Vaccine Forum (IIMVF)).

When preparing your application, the following points should be noted.

- This R&D area aims to understand the mechanisms of immunological memory in humans, so your research plan needs to use human clinical samples. Research plans that use only animal models will not be recommended. Ideally, ethical approval for the use of human samples will have already been given at the time of application, but if more time is needed for approval, please ensure that the plan includes details on how ethical approval will be obtained and how much number of samples will be analyzed, etc. If the proposal is selected, please implement the next steps to apply for and obtain ethical approval without delay.
- Please formulate a hypothesis that will be proved during the research period, and clearly specify the milestones to be achieved at the interim and end points of the project, as well as plans for obtaining intellectual property rights. Please include alternative plans if results are not obtained as expected. Rather than investigations on an extension of existing research, we expect innovative proposals that may create new concepts in the field of immunology.
- Please include preliminary information that can support assessment of whether the research plan is feasible and the hypothesis is rational.

○ 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.

Briefing of solicitation

Please check the following site for more information on the briefing of solicitation (NOTE: Briefing will be only in Japanese.).

https://www.amed.go.jp/en/news/program/1602B_00022.html

3.2.4 Integrated understanding of multi-sensing networks and elucidation of their control mechanisms leading to the innovation of medical technologies

Program Supervisor (PS): Ryozo Nagai, President, Jichi Medical University

Program Officer (PO): Shoji Takeuchi, Professor, Graduate School of Information Science and Technology, the University of Tokyo

Program Officer (PO): Kohji Nishida, Professor, Graduate School of Medicine, Osaka University

* R&D Area for the Research and Development Objective "Integrated understanding of human multi-sensing networks and elucidation of their control mechanisms" (page 119)

Outline of the Research and Development Area

This R&D area targets the development of an integrated understanding of multi-sensory systems that includes sensory systems and peripheral nerve networks, as well as visualization of activity and the development of control methods.

The sensory organs and central nerves (brain), the internal organs (including the stomach, intestines, and liver), and the peripheral nerves that are widely distributed throughout these areas are anatomically and functionally related, and they all work together in a coordinated manner, playing important roles in maintaining various functions in the body. In recent years, it has become clear that deteriorated or lost sensory functions or peripheral neuropathy, triggered by aging or internal/external stress, not only reduce quality of life (QOL) because of the resulting functional disorders, but are also involved indirectly or directly in the onset or progression of diseases such as cancer, dementia, or lifestyle diseases. An integrated understanding of multi-sensory physiological mechanisms comprising these sensory systems and peripheral nerve networks could lead to the development of new treatment methods targeting various diseases or organs across the body, resulting in improved QOL and longer healthy life expectancies. Furthermore, the origination of innovative technologies to control multi-sensory systems and their real-world application is expected to contribute significantly to achieving a society of abundance and wellbeing through sensory substitution or shared sensory applications.

This R&D area will bring together researchers from different fields, including medicine, biology, engineering, materials science, and informatics, and will foster collaborations to drive research related to developing an integrated understanding of multi-sensing networks and creating seeds for healthcare innovation. This R&D area will also promote research to clarify the impact of reduced multi-sensory system function on homeostasis in the body, with a view to overcoming human disease, and research to investigate basic principles of multi-sensory integration through which individual sensory functions interconnect. Furthermore, in order to establish analytical technologies for clarifying these physiological functions and to apply findings for healthcare purposes, this R&D area will promote multidisciplinary collaboration for the development of new therapeutic methods mediated via the sensory organs and nerves, as well as innovative research and development relating to the measurement, control and use of biological signals by fully applying engineering technologies in new devices.

Under the shared Research and Development Objective "Integrated understanding of human multi-sensing networks and elucidation of their control mechanisms" established by the Japan Agency for Medical Research and

Development (AMED) and the Japan Science and Technology Agency (JST), this R&D area will initiate four programs simultaneously (the AMED-CREST and PRIME programs run by AMED, and the CREST and PRESTO programs run by the JST) and researchers in these programs will work in collaboration to conduct research. The AMED programs will promote research that contributes to originating seeds for innovative healthcare and basic research with a view to achieving outcomes in health and healthcare applications. The JST programs are aimed at expanding sensory functions or obtaining new functions, with a focus on the development of infrastructure or applied technologies to elucidate basic principles and roll out real-world applications.

Coordination between these four programs will provide forums for the exchange of opinions on an ongoing basis, and promote opportunities for organic collaborations such as joint researches and creating lifelong friendships through research. In terms of coordination outside of these four programs, under the leadership of the Program Supervisor (PS), joint symposia and workshops will be proposed and organized, including at research seminars, meetings, and academic conferences in Japan and overseas, and support will be provided for partnerships with overseas research institutions and organizations, as well as initiatives to promote the spread of new research areas originating in Japan such as proposals for special editions in international scientific journals etc. on this research theme.

Furthermore, activities will be undertaken with a view to forming connections with the Moonshot Goal #2 “Realization of ultra-early disease prediction and intervention by 2050” in the Moonshot Research and Development Program (2020–29) and AMED’s Strategic Research Program for Brain Sciences/Brain Mapping by Integrated Neurotechnologies for Disease Studies/Strategic International Brain Science Research Promotion Program (from the 2021 academic year to the 2029 academic year).

Through these activities it is anticipated that other unexpected results will be obtained in addition to promoting proposed plans.

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

This R&D area aims to clarify the mechanisms of action in multi-sensory systems and develop technologies to visualize and quantify activity status; clarify disease pathology based on these mechanisms breaking down; develop therapeutic and preventive methods that produce few side effects and create pharmaceuticals, medical equipment, and measuring and control devices tailored to individuals. At the same time, we are calling for research proposals aimed at creating seeds for innovation by expanding the body’s multi-sensory functions and applying advanced sensory mechanisms.

This R&D area is implemented by AMED and JST together, with the two organizations liaising closely to promote the research. In this research area, researchers from the four AMED and JST programs will create a network-based research institute, and in so doing will advance mutual collaboration between young researchers and encourage further development of research.

* Agreement for the sharing of the proposal with JST

This R&D area is a cooperative research area with JST. AMED may share the proposal with JST during the selection process. Please submit the proposal documents after confirming and agreeing with AMED’s sharing the proposal with JST.

(1) AMED-CREST (unit-type)

For this R&D area, we call for innovative research proposals that will use a transdisciplinary approach to clarify the mechanisms of action in multi-sensory systems, including sensory systems and peripheral nerve networks; clarify disease pathology; develop technologies to visualize and quantify activity status; and use these technologies to develop therapeutic and preventive methods. We also welcome research proposals for the creation of seeds for basic engineering technology to further our understanding of the anatomical structures and physiological functions of sensory organs and peripheral nerve networks and clarify the mechanisms of molecular regulation through nerve control. R&D PIs do not necessarily have to be active in the medical field but can also be from engineering and other fields.

To pursue these research themes, we look for the formation of research units that bring together various different fields of research, such as neurology, physiology, molecular biology, cell biology, regenerative medicine, clinical medicine, tissue engineering, materials science, information science, and micro-mechatronics. For research proposals aimed at developing new technologies to visualize, quantify, and control sensory system activity, we welcome proposals that build research systems comprised of researchers from medical and biological disciplines and as well as from engineering disciplines; that foster active partnership between these disciplines; and that pursue the development of bioelectronic medicines, wearable devices, human interface, implantable devices, organ chips, micro-electro mechanism systems (MEMS), or microfluidic device and other technologies.

Below we provide examples of anticipated R&D proposals, but we are looking for world-class, innovative research proposals that go beyond these examples.

- Clarification of metabolic, immune, and endocrine mechanisms etc. involved in homeostasis, the mechanisms that maintain brain function, and the mechanisms behind disease onset that involve the multi-sensing network
- Clarification of the mechanisms of neurologic dysfunction accompanying chronic disease, lifestyle disease, stress, and aging, and research that will contribute to methods to prevent these dysfunctions and help to maintain/promote good health
- Clarification of the mechanisms involved in diseases relating to the sensory organs (including the five senses, perception, and sense of position and vibration) and peripheral nerve networks
- R&D that will contribute to the creation of various modalities of medical technology to compensate for sensory organ dysfunction
- Development of innovative device technologies to measure and control sensory organ and nerve activity in humans or animal models
- Devices targeting the nervous system, medical device development, and technology development for rehabilitative and surgical operative methods
- Development of devices and equipment for the measurement, control, and use of biological signals (does not have to be signals that directly involve the nerves)
- Development of organ chips that recreate sensory organs or nerve systems in vitro
- Development of innovative measuring and control technologies that apply the mechanisms of action of multi-sensory systems

○ 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.

○ In this R&D area's AMED-CREST (unit-type), it is exceptionally permitted to apply duplicately to the JST CREST research area "Research on Multi-sensing Biosystems and Development of Adaptive Technologies" launched under the same R&D objective. However, applicants are requested to submit R&D proposals to both AMED and JST using the specified AMED-CREST and JST CREST forms, respectively. If proposals are made using the incorrect forms they will not be accepted. Furthermore, there will be no simultaneous adoption of proposals in the AMED R&D area and the JST research area.

(2) PRIME (solo-type)

The PRIME program involves research performed by an individual researcher in their specialist field. We invite proposals in the R&D areas as described in the AMED-CREST program, particularly for highly innovative research. We are calling for a wide range of proposals aimed at achieving an integrated understanding of multi-sensory systems and their medical applications, including challenging topics that may open up new frontiers of research such as clarification of the mechanisms of sensory signal response and development of devices to measure and control biological signals; research to create novel technologies that may make significant contributions to basic research; and exploratory technology development to allow minimally invasive evaluation of various biological signals. For engineering proposals in particular, there is no need to demonstrate at the time of proposal submission how the research will specifically connect to healthcare. We are looking for proposals for unique devices or systems based on novel perspectives. Note that after a research proposal is selected, we will provide support for developing connections with medical researchers in the field under research or other areas as the research progresses.

Under the PRIME program, researchers are not necessarily expected to produce evidence at the end of the research period demonstrating links to the development of healthcare applications. We expect proposals for challenging projects that might prompt a paradigm shift in health, prevention, and healthcare in the future. During the research implementation process, we will look for a proactive approach by the applicant to developing networks, regardless of the applicant's specialty, with a view to further developing the research in the future. This may include interacting with other research groups in the same or different fields, researchers in AMED-CREST research units, and researchers participating in CREST and PRESTO programs run by the JST.

○ 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.

○ Regarding PRIME program (solo-type), as an exceptional measure, it is possible to submit duplicate application with JST's PRESTO "Multisensory Integration in Biological Systems" research area, which is established under the same R&D objective. Please note that each application shall be done with using the format specified by AMED (PRIME) and JST (PRESTO) for the proposal. If the proposal form error happens, it will not be accepted. Also, it will not be selected in two areas at the same time.

Here to download information on the briefing of solicitation and the application document (graphical abstract)

The submission of the graphical abstract is highly encouraged in this R&D area. The graphical abstract serves as helpful material in the reviewers' understanding of the content.

With regard to the downloading of information on the briefing of solicitation and the application document (graphical abstract), notification is provided on the following AMED websites.

Briefing of solicitation (NOTE: Briefing will be only in Japanese.)

https://www.amed.go.jp/en/news/program/1602B_00022.html

Application document (graphical abstract)

https://www.amed.go.jp/program/list/16/02/001_MultiSensing.html (in Japanese)

3.2.5 Generating research infrastructure and novel technologies for anti-infective drug and vaccine discovery

Program Supervisor (PS): Yohei Doi, Professor, Departments of Microbiology and Infectious Diseases, Fujita Health University School of Medicine / Professor, Division of Infectious Diseases, University of Pittsburgh School of Medicine

Program Officer (PO): Yoshiharu Matsuura, Director, Center for Infectious Disease Education and Research (CiDER) and SA Professor, Laboratory of Virus Control, Research Institute for Microbial Diseases (RIMD), Osaka University

* R&D Area for the Research and Development Objective “New approaches in drug and vaccine discovery for infectious diseases” (page 123)

Outline of the Research and Development Area

COVID-19 has spread around the world with extremely serious consequences. It is anticipated various other infectious diseases are likely to occur in Japan in the future. Antimicrobial-resistant (AMR) pathogens are also a major concern, where as many as 10 million people are projected to die annually by infection from AMR pathogens globally by 2050 if nothing is done to address this issue, possibly outstripping the number of deaths due to cancer. It is clear that controlling infectious diseases remains one of the most urgent challenges facing us today.

There are various challenges that are specific to the field of infectious diseases, including the diversity of pathogens, difficulty achieving complete cure for latent infections, inability to forecast epidemics, and the need for an immediate response when a disease does spread. In order to control emerging and re-emerging infectious diseases, in-depth understanding of the pathogens involved and the interactions with the host is a prerequisite to the development of prophylactic, diagnostic, and therapeutic interventions. Furthermore, there is a need to accelerate the processes required for clinical application of such agents, with ongoing review of the research targets, scope of research, and systems for collaboration. In Japan, however, various factors combine to hamper infectious disease drug discovery research and development, including inadequate research funding, a dearth of early career investigators, lack of collaboration between investigators across scientific fields, and withdrawal of pharmaceutical companies from infectious disease research.

The goal of this R&D area is to establish technologies and infrastructure to accelerate basic research in the field of infectious disease drug discovery. Specifically, this program aims to leverage various research methodologies and resources (e.g., cryoelectron microscopy, in silico analytical technologies, supercomputers, big data, patient samples) and networks of investigators and domestic infectious disease research sites supported by AMED and other bodies. The program also encourages interdisciplinary research through coordinated collaborations between research institutions and pharmaceutical companies in Japan and overseas and active participation of investigators in a wide range of fields not limited to infectious diseases or microbiology. It is hoped that these efforts will lead to development of new drug discovery modalities, optimization of existing modalities, and support development of new platform technologies, with the goal of accelerating infectious disease drug discovery.

In addition, this R&D area provides opportunities for research exchanges with researchers who were awarded AMED's Japan Program for Infectious Diseases Research and Infrastructure (Interdisciplinary Cutting-edge Research) since FY2021, promoting discussions between projects and the launch of joint research, as well as active collaborations between programs.

* Calls for proposals relating to the FY2023 Japan Program for Infectious Diseases Research and Infrastructure (Interdisciplinary Cutting-edge Research)
  https://www.amed.go.jp/koubo/15/01/1501B_00072.html (in Japanese)

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

This R&D area aims to resolve issues that are bottlenecks in the basic research phase of infectious disease drug discovery by combining existing drug discovery seeds, infrastructure/technologies, research resources for the discovery of drugs against infectious diseases caused by pathogens including bacteria, fungi, and viruses, and developing an array of robust drug discovery modalities that ultimately translates to clinical application, as well as strongly promoting interdisciplinary research. Another key objective is to support early career investigators who specialize in infectious disease drug discovery as part of an effort to build a cohort of investigators capable of applying their expertise to respond immediately when new infectious diseases emerge in the future. We call for research proposals in the following specific areas: (1) develop new approaches, including drug discovery modalities, that will contribute to the prevention and treatment of infectious diseases; (2) optimize existing modalities for infectious disease drug discovery; and (3) develop technology platforms that will accelerate infectious disease drug discovery and generate innovative preventive and therapeutic agents against infectious diseases.

In this R&D area, we hope to receive proposals from, and see participation by, a large number of promising early career investigators. We also welcome proposals that include collaborations with investigators at overseas research institutions engaged in advanced research via existing or new networks.

AMED-CREST (unit type)

The aim of this R&D area is to build a strong network of researchers and platforms for drug discovery and development in order to ensure the health and safety of domestic residents and protect them from infectious diseases that are expected to emerge or propagate after the COVID-19 pandemic in Japan. We also welcome research proposals from teams of investigators encompassing various scientific fields, not limited to infectious diseases and microbiology, including, but not limited to, immunology, organic chemical synthesis, imaging, genomics, bioinformatics, structural biology, animal experiments, and mathematical modelling. We also welcome research proposals that combine different areas of cutting-edge research and involve coordinated collaborations with research institutions and pharmaceutical companies in Japan and overseas in order to create new modalities, optimize existing modalities, build platform technologies for drug discovery research and development, and establish high-quality and efficient evaluation methods of drug discovery targets.

Below we provide examples of potential proposals. We also seek innovative research proposals that go beyond these examples.

- Basic research that may lead to the discovery of new preventive and/or therapeutic agents, based on insights of pathogenesis, from pathogen entry into the body to arrival at the target tissues, interactions with intracellular organelles, and the pathway by which infection is established including proliferation within the cells.
- Establishment of novel therapeutic concepts and development of modalities through elucidation of epigenetic control governing pathogen proliferation, the role of microbiome, and pathogen-specific host defense mechanism.
- Exploratory research aimed at development of novel antimicrobials (small molecules, natural substances, other entities) that target the pathogens' virulence, such as control of the bacterial toxin secretion system or quorum sensing transcription factors.
- Elucidation of the mechanisms of drug resistance in bacteria, fungi, or viruses that cause sexually transmitted and other infectious diseases, as well as research into the mechanisms of long latency and persistent infections, and the use of these findings to establish new therapeutic concepts.
- Development of technology platforms for antimicrobial drugs, including nucleic acid therapeutics, peptides, nanobodies, and compounds that induce targeted protein degradation.
- Development of research platforms aimed at understanding the mechanism of drug resistance and development of pharmaceutical agents to inhibit or counter relevant mechanisms of resistance.
- Research of drug discovery infrastructure targeting drug-resistant fungal infections.
- Research to build exploratory infrastructure to search for innovative protective antigens against pathogens for which no effective vaccines are currently available or more effective vaccines are needed and develop suitable vaccine modalities.
- Development of infectious disease animal models that can be used for clinical prediction and alternative humanized models, including in humanized mice, chimeras, and human tissues of iPS cell origin.
- Refinement of in silico screening using pathogen protein structural analysis and protein science, and research aimed at rational drug design for compound optimization. In addition, research to dramatically shorten infectious disease drug discovery by demonstrating correlation between in silico and wet studies.
- Development of infectious disease drug discovery AI platforms through the use of big data that can draw on Reverse Translational Research (rTR), multi-omics analysis, and other relevant areas.
- Development of analytical methods using biostatistics and biomathematics and of platform technologies for prevalence prediction, through the use of databases on pathogen evolution and genome mutations to identify pathogen immune evasion mechanisms, optimize natural host symbiosis, and predict emergence of variant or resistant strains. Also, development of modalities to enable immediate response.

When responding to this call for proposals, please note the following points when submitting a research plan.

- Clearly state the research hypotheses and goals and objectives.
- Clearly indicate how the various research projects run by the PI and the Co-Investigators could generate synergistic effects and how this will contribute to the goals and objectives for the overall research proposal.
- Formulate a research plan that can be executed within the R&D period and include specific steps to be taken if the research does not progress as planned.

- While drug discovery research targeting a specific infectious disease is not the main scope of this R&D area, applicants may include such research plans as proof of concept in the proposal.
- For research based on SARS-CoV-2, design the research proposal with a focus on applications in other emerging pathogens.
- We encourage collaborations between different scientific disciplines that are logical and innovative.
- We strongly encourage proposals where early career investigators take on leading roles.
- We welcome proposals designed to include collaborations with investigators at overseas research institutions engaged in advanced research via existing or new networks.
- This program does not include development phases beyond non-clinical studies, but research can be progressed through out-licensing to other programs according to the status of R&D progress.
- Given the goals of the R&D, we recommend participation of physician scientists involved in clinical practice in the relevant field.

○ 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 (in principle, up to five-and-a-half years).

Briefing of solicitation

Please check the following site for more information on the briefing of solicitation (NOTE: Briefing will be only in Japanese.).

https://www.amed.go.jp/en/news/program/1602B_00022.html

Chapter 4. Schedule, Review Method, etc.

4.1 Period of Acceptance of Proposal Documents/Selection Schedule

The period of acceptance of proposal documents and selection schedule is, as at the time that the call for applications opens, planned as follows.

Period of acceptance of proposal documents/ selection schedule (Please be sure to bear in mind Notes 1. to 12.)	
Period of acceptance of proposal documents	From Tuesday, April 11, 2023 to Tuesday, May 30, 2023 at noon (JST) (Observe strictly)
Document review	From middle July 2023 to late July 2023 (tentative)
Hearing review	Once the schedule for the hearing reviews has been decided upon, applicants will be informed via the Calls for Proposals page on the AMED website indicated below. https://www.amed.go.jp/en/news/program/1602B_00022.html **Elucidation of mechanisms for stress responses to disease development** AMED-CREST From late July 2023 to middle August 2023 (tentative) PRIME From late July 2023 to middle August 2023 (tentative) **Bridging the fundamental mechanism of aging and the effective treatment of age-related disease associated with impaired functional system** AMED-CREST From late July 2023 to middle August 2023 (tentative) PRIME From late July 2023 to middle August 2023 (tentative) **Immunological memory: Understanding, regulation and medical innovation** AMED-CREST From late July 2023 to middle August 2023 (tentative) **Integrated understanding of multi-sensing networks and elucidation of their control mechanisms leading to the innovation of medical technologies** AMED-CREST From late July 2023 to middle August 2023 (tentative) PRIME From late July 2023 to middle August 2023 (tentative) **Generating research infrastructure and novel technologies for anti-infective drug and vaccine discovery** AMED-CREST From late July 2023 to middle August 2023 (tentative)

Notification of selection/rejection	Early September 2023 (tentative)
Date of commencement (contracting, etc.) of R&D Project	Sunday, October 1, 2023 (tentative)

Note 1. For all proposals documents, the documents received after the deadline will not be accepted.

Note 2. If not completed correctly, proposal documents may not be accepted.

Note 3. When human WGS analysis is conducted, proposal documents will not be accepted unless the Human Whole Genome Sequence Analysis Protocol Form is submitted.

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. Hearing reviews may sometimes be conducted over the Internet etc.

Note 6. In the case that a hearing review is conducted, the PI for the relevant project shall as a general rule be contact by e-mail no later than one week before the hearing is to take place. (In the case that the project is not eligible for a hearing review or hearing reviews 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 hearing reviews, this will be posted on the Application Information page on the AMED website listed in Chapter 5, so please refer to this page for details. Note that we will not answer questions regarding the eligibility of individual projects for hearing reviews.

Note 7. The PI may be sent via e-mail a list of matters of inquiry that have arisen through the document review process. Please respond promptly to these matters of Inquiry by the deadline designated by AMED at the time of inquiry via the method designated by AMED.

Note 8. As a general rule, the hearing review shall be attended by the PI only and the accompaniment of others not permitted. The date and time of the hearing review cannot be changed. It should be noted that interviews will in principle be conducted in Japanese, but that English may be used when conducting the hearing in Japanese is impractical.

Note 9. Following the hearing review, administrative matters may be confirmed with the PI as necessary. Please respond swiftly to the relevant checks via the method specified by AMED.

Note 10. The method of hearing reviews may be altered or cancelled due to unforeseen circumstance such as social disorder caused by outbreaks of infectious diseases, natural disasters or other reasons. In addition, in the event that hearing reviews are cancelled the period for the document review may be extended.

Note 11. 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.

Note 12. The tentative date of the commencement (contracting, etc.) of R&D project has been set in consideration of the time period required for formulating an optimal R&D plan at the time of submitting the proposal with a view to the timing of the commencement of R&D, and to enabling researchers to make the preparations they can between the time of the decision to adopt the project and the time the 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 institutions, 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.

4.2 Method for Reviewing Proposal Documents

4.2.1 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 Project Evaluation Panel members 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 will evaluate the stipulated evaluation items, based upon which AMED decides the projects to be awarded.

(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 hearing reviews as necessary and deliberating on the project content. Please not that, 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. Furthermore, 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 9 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) Project 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 and the names of the PIs will be published at a later date on the AMED website. Furthermore, as a general rule, the names of all Project Evaluation Panel members shall be published by AMED once each year. (For details about publication on the AMED website, please refer also to Chapter 6.)

(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.

i) The evaluatee is a family member/relative of the Project Evaluation Panel member.
ii) The evaluatee is affiliated with the same department at a university, the National Research and Development Agency, or a national research institute or other research institution or business enterprise as the Project Evaluation Panel member.
iii) The evaluatee has worked closely with the Project Evaluation Panel member on a joint research project within the past three years including the fiscal year in which the Project Evaluation Panel evaluation is conducted.
iv) 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.
v) 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.
vi) The Project Evaluation Panel member is in a direct competitive relationship with the evaluatee.
vii) 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 and staff members, PD, PS, PO, or Project Evaluation Panel members regarding evaluations or project selection.

(I) From the perspective of verifying the appropriateness of R&D management, AMED may require submission of the materials regarding management of R&D for drugs,1 regenerative medicine, etc.2 and medical devices.3 In addition, inquiries may be made regarding the content of these materials as necessary. Please refer to the following web pages for more details.

[1] https://www.amed.go.jp/koubo/iyakuhin_check.html (in Japanese)

[2] https://www.amed.go.jp/koubo/saisei_check.html (in Japanese)

[3] https://www.amed.go.jp/koubo/medical_device_check.html (in Japanese)

(J) In the course of this program there may be cases in which, from among the AMED research expenses received in the past by applicants, reviews are conducted of the submitted proposal documents based on the Mid-term Reviews and Ex-Post Evaluations of R&D projects put to use to create the current project proposal.

4.2.2 Review Criteria and Perspectives in Evaluating Projects

In selecting projects for this program, reviews of proposal documents shall be carried out from the following perspectives. In the case that a proposal is submitted for an R&D project that designates a subsidiary institution,

evaluations shall also examine the necessity of the subsidiary institution for carrying out the R&D and the competency of the subsidiary institution to carry out the R&D.

(A) Compatibility with the program's purpose

- Is the project compatible with the program's purpose and objectives, etc.?
  (Does the project contribute to the achievements of the R&D objective? In addition, is the project compatible with the purpose of the R&D Area?)

(B) Scientific/technological significance and advantage

- Does the project proposal have originality and novelty?
- 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?
- In the case of PRIME, is the basic research regarded as challenging and is development at a high level by international standards also expected?

(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? Also, does the applicant show promising preliminary results for realizing the R&D concepts?)
- Is the project plan in compliance with laws and ordinances related to bioethics or safety measures?
  * Please take particular note of the fact that the Ethical Guidelines for Life Science and Medical/Health Involving Human Subjects were partially revised on March 10, 2022.
    https://www.mext.go.jp/b_menu/houdou/mext_00950.html (in Japanese)

(D) Implementation system

- Has an R&D system centered on the applicant been organized appropriately?
- Has a sufficient collaboration network been constructed?
  (In the case of AMED-CREST, does the R&D Co-Investigator play an essential role in realizing the R&D concepts? Has the collaboration framework been constructed sufficiently to enable the R&D Co-Investigator to significantly contribute to the achievement of the R&D goals?)
- In the case of PRIME, is the scale of implementation appropriate for R&D conducted by individuals?
- 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 concepts 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?

4.3 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 for other AMED programs.

Chapter 5. Preparation and Submission Method of Proposals, etc.

5.1 Preparation of Proposal Documents

5.1.1 Proposal Documents Necessary for Application

The following forms are required for the application. Note that the forms necessary for submissions vary between research types (AMED-CREST or PRIME). Be sure to fill out each item in the forms concisely and clearly. With regard to the acceptance period for proposal documents and submissions, please refer to Chapter 4.

All R&D areas for unit-type (AMED-CREST)

No.	Mandatory or optional	Necessary proposal documents	Remarks
1	Mandatory	(Form C1) R&D Proposal[1]	
2	Mandatory	(Appendix C1) Summary of Proposal (Japanese/English)	
3	Mandatory when applicable	(Appendix C2) Human Whole Genome Sequence Analysis Protocol Form[2]	When conducting human WGS analysis

[1] In the FY2023 selection process, the proposals will not be peer-reviewed by researchers affiliated with overseas research institutions (international reviewers). Therefore, it will not be necessary to submit the English Proposal Form and the Security Trade Control Checklist.

[2] In the event that whole human genome sequence analysis or whole exome sequencing analysis is included in the research plan, submission of Appendix C2 “Human Whole Genome Sequence Analysis Protocol Form” is mandatory. It should be noted that according to the content of the protocol form certain submissions may be treated as ineligible for review. In the event that whole human genome sequence analysis or whole exome sequencing analysis is included in the research plan, please contact the applications secretariat (kenkyuk-kobo@amed.go.jp) by no later than Tuesday, May 9.

All R&D areas for solo-type (PRIME)

No.	Mandatory or optional	Necessary proposal documents	Remarks
1	Mandatory	(Form P1) R&D Proposal	
2	Mandatory	(Appendix P1) Summary of Proposal (Japanese/English)	
3	Mandatory when applicable	(Appendix P2) Human Whole Genome Sequence Analysis Protocol Form[1]	When conducting human WGS analysis
4	Mandatory when applicable	Additional form for duplicate application (Japanese Only)[2]	When making a duplicate application for PRIME (solo-

	(Only for the Aging R&D area)		type) of the AMED R&D area “Bridging the Fundamental Mechanism of Aging and the Effective Treatment of Age-related Disease Associated with Impaired Functional Systems” and the JST PRESTO research area “Fundamental Understanding of Age-Related Organismal Transformations”

[1] In the event that whole human genome sequence analysis or whole exome sequencing analysis is included in the research plan, submission of Appendix P2 “Human Whole Genome Sequence Analysis Protocol Form” is mandatory. It should be noted that according to the content of the protocol form certain submissions may be treated as ineligible for review. In the event that whole human genome sequence analysis or whole exome sequencing analysis is included in the research plan, please contact the applications secretariat (kenkyuk-kobo@amed.go.jp) by no later than Tuesday, May 9.

[2] When making a duplicate application for PRIME (solo-type) of the AMED R&D area “Bridging the Fundamental Mechanism of Aging and the Effective Treatment of Age-related Disease Associated with Impaired Functional Systems” and the JST PRESTO research area “Fundamental Understanding of Age-Related Organismal Transformations,” it is necessary to submit the “Additional form for duplicate application (Japanese Only).” The Forms shared by the AMED and JST secretariats as submitted items, and serve as referential materials for the selections made under both programs. The format of the “Additional form for duplicate application” is the same for PRIME and PRESTO, and it is posted on the PRESTO Call for Research Proposals pages*. When making a proposal to PRESTO, please submit it via e-Rad in conjunction with your R&D Proposal. (Since the form will be shared with JST and AMED, there is no need to submit it to AMED. Please refer to the PRESTO Call for Research Proposals pages for more details.) In the event that the “Additional form for duplicate application” is not submitted despite a duplicate application being made to PRIME and PRESTO, both PRIME and PRESTO will regard the application as unaccepted. Applicants are requested to submit R&D proposals to both AMED and JST using the forms respectively stipulated by AMED and JST. If proposals are made using the incorrect forms, they will not be accepted. In addition, there will be no simultaneous adoption of proposals in the AMED R&D area and the JST research area.

* JST “Fundamental understanding of age-related organismal transformations”
https://www.jst.go.jp/kisoken/boshuu/teian/en/top/ryoiki/ryoiki_p09.html

5.1.2 Methods for Obtaining Proposal Forms

Please download the forms for proposal documents that AMED has prepared from the "Calls for Applications" page on the AMED website.

https://www.amed.go.jp/en/news/program/1602B_00022.html

5.1.3 Proposal Document Forms and Notes for Preparation

(1) Preparation of Proposal Documents

Please be careful with regard to the following items when inputting information into the proposal document forms.

As a general rule, the R&D Proposal is to be prepared in Japanese and English, 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.

(A) With regard to forms prescribing word limits or page limits, please be sure to comply with the set limits. Even if there are no page limits please complete as concisely and clearly as possible.

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

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

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

(E) 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.

(2) 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 11.

(3) Approval of R&D Project Proposals by Affiliated Research Institutions

In submitting proposal documents, the PI must obtain the approval of the Principal Institution (research institution with which the PI is affiliated and which is to conclude a direct contracted agreement with AMED). Furthermore, in the case that multiple research institutions jointly submit an R&D proposal for carrying out research,. obtain the approval of all the institutions and then note in the R&D Proposal that approval has been obtained. (Change the □ in the proposal to ■).

(4) 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.

(5) Ineligible Project Proposals

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

(A) Proposals that aim simply to purchase ready-made facilities and equipment.

(B) 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.

(6) Submission of Human Whole Genome Sequence Analysis Protocols

In research projects conducting human whole genome sequence (WGS) analyses (Please refer to Chapter 2, 2.5.6 “Data Sharing.”), it is necessary to show each item of the protocol by submitting the prescribed form. In the event that the form for the project in questions is not submitted, the applications will be treated as “not accepted” and will not be subject to screening. Please check with sufficient care whether or not human WGS analyses will be conducted in the course of the proposed project.

Furthermore, even in the event that the prescribed forms are submitted, R&D projects that fail to satisfy the conditions stated in Chapter 2, 2.5.6 “Data Sharing” will be treated as “not adopted.”

5.2 Required Proposal Documents Apart from R&D Proposals

(1) Human Whole Genome Sequence Analysis Protocol Form

In cases in which human WGS analysis is conducted, the submission of the Human Whole Genome Sequence Analysis Protocol Form is mandatory. With regard to the details of sequence data and protocol information, refer to Chapter 2 “Application Requirements.”

(2) Records of 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 or other consultation services, and if the applicant has already undergone face-to-face advice, a record of the face-to-face advice or separate sheet (consultation content) should be submitted with the R&D proposal.

It should be noted that, even in the event that face-to-face advice has not been conducted, if a schedule for face-to-face advice has been decided upon the applicant is requested to write on the proposal “schedule for planned face-to-face advice.” (As PMDA does not keep any records of preliminary consultations, please do not attach any documentation detailing whether or not they have been implemented, or any other documentation such as the minutes or outlines of preliminary consultations created by academia.)

Note: R&D projects moving into the practical application stage (R&D projects that are within the target scope of the regulatory science strategy consultation or other PMDA consultation services) are, as a condition of adoption, required to implement each clinical trial according to the research plan agreed in advance at the regulatory science strategy consultation or other consultation services (face-to-face advice) provided by the Pharmaceuticals and Medical Devices Agency (PMDA). 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.

(3) Materials related to clinical study, etc.

For research undertaking clinical trials or clinical studies with a view to creating innovative drugs, medical devices etc., or nonclinical studies aimed at conducting such trials/studies,[1] applicants are required to submit a trial plan and protocol[2] (including information such as aims, subjects, selection criteria, exclusion criteria, number of cases, observation content, intervention content, statistical methods, and research system) and other materials

related to the clinical study (free format; a draft may be submitted if the trials have not been implemented at the time of application).

[1] Does not include clinical research that is not aimed at creating new drugs or medical devices, etc. or that differ from normal processes for evaluating/approving new medical technology.

[2] In the course of protocol creation please refer to the following as necessary. (As they are for illustrative purposes they do not provide all-encompassing coverage of clinical trials.)

- Center for Clinical Trials, Japan Medical Association (procedural manuals on the creation of protocols and clinical report forms (CRF))
  http://www.jmacct.med.or.jp/clinical-trial/enforcement.html (in Japanese)
- Japan Medical Association Ethical Review Board (sample retrospective observational study protocols)
  https://www.med.or.jp/dl-med/doctor/s_sien/rei_keikakusyo.doc (in Japanese)
- Translational Research Center for Medical Innovation, Foundation for Biomedical Research and Innovation at Kobe (guidelines on the creation of investigator-initiated clinical trial protocols)
  Randomized controlled trials
  https://www2.tri-kobe.org/support/download/protocol_summary2.pdf (in Japanese)

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

With regard to research institutions 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; partially revised on February 20, 2015), based on these fundamental guidelines, research institutions may be required to submit a copy of the results of their most recently implemented self-monitoring/self-evaluation related to the research institution's conformance with these fundamental guidelines.

(5) Materials 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.

5.3 How to Submit Proposal Documents

Please submit proposal documents via e-Rad by the deadline. It should be noted that web access increases shortly before the deadline and errors sometimes occur, so allow yourself plenty of time for submission. Applications will not be accepted if the proposal documents are not submitted by the deadline. In order to amend proposal documents that have already been submitted, you need to carry out "Retrieval" procedures during the acceptance period and then re-submit the amended documents before the application deadline. (For details regarding retrieval procedures, please refer to the Manuals for Researchers, which can be found at the e-Rad portal site (https://www.e-

rad.go.jp/en/manual/for_researcher.html)) Please note that submitted proposal documents cannot be replaced after the application deadline.

Note 1: The e-Rad system is available for use between 00:00 and 24:00 on weekdays and public holidays. Please note that the operation of the e-Rad site is sometimes suspended during operating hours due to maintenance or inspections. In the event that e-Rad is to be temporarily shut down, notice will be posted in advance on the e-Rad portal site.

Note 2: Proposal document files should, with the exception of where specified, be uploaded in a PDF format. 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.

Note 3: The maximum size of single files that can be uploaded is 15MB.

5.3.1 Checking Acceptance Status on e-Rad

Verifying the acceptance of proposal documents can be done by going to the "Submitted proposals" section on the e-Rad site and looking at the Project list page. Proposal documents whose application status has not changed to "Processing (Funding Agency) /Application in progress" or "Accepted" by the deadline will become invalid. In the event that although a researcher has submitted the proposal documents prior to the deadline and acknowledgment has been given by the clerical affairs supervisor their status has not changed to "Processing (Funding Agency) /Application in progress" or "Accepted," please contact the division in charge of this program. It should be noted that in order for the funding agency to manage the project applications it is necessary that they are "accepted" by the funding agency but from the perspective of the application actions taken by researchers themselves it is not necessary for them to proceed to the "accepted" by the funding agency stage. If by the end of the acceptance period the state of the project application is shown as "Application in progress," and the application type (status) as "Processing (Funding Agency) /Application in progress," the application in question can be regarded as having been normally completed.

Note that in the event that there is a fault in the e-Rad system during the application period, there may be Notices from Funding Agencies or Notices from System Administrator displayed on the screen after logging in to e-Rad, or related information displayed on the top page of the AMED website, so please check these details.

Application status	Application type (status) display
i) Application submitted	The application type (status) will change to "**Processing (Research institution) /Application in progress**," which indicates that the acknowledgement by the research institution is still unfinished. (Application to the program is not complete at the point that the PI submits the application to their affiliated research institution via e-Rad. Be sure to undergo procedures to obtain approval of the submission of the R&D project from your affiliated research institution) In the event of difficulties in the procedures for the acknowledgement by the research institution please consult with the division in charge of this program.

ii) Procedures for acknowledgement by the research institution completed	The application type (status) will change to "**Processing (Funding Agency) /Application in progress.**"
iii) Accepted by the funding agency (AMED)	The application type (status) will change to "**Accepted**."

5.3.2 Points to Note in Using e-Rad

(1) Prior registration of research institution

In the case that researchers are applying for the program through a research institution, the "Principal Institution" and "Subsidiary Institution" must be registered with e-Rad prior to the time of application as a general rule. For information regarding how to register research institutions, 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 go through the procedures at the research institution registration application page (https://www.e-rad.go.jp/organ/entry.html).

*Registration may require several days, so please allow leeway of two weeks or more for carrying out procedures.

*Please note that once you have registered your affiliated institution with e-Rad, there is no need for you to register it again for R&D programs or projects under the jurisdiction of other ministries or agencies.

*If you have already registered it 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 it again.

*In the case that you are not affiliated with a specific research institution at the time of application or are affiliated with a research institution outside of Japan, please separately contact the division in charge of this program as early as possible before submitting your application.

(2) Prior registration of researcher information

The PI, an applicant, and the Co-Investigators participating in the research must obtain a login ID and password.

The clerical affairs supervisor should register information for researchers who are affiliated with the research institution. The clerical affairs supervisor logs into e-Rad using the ID and password obtained through the procedures in (1) above, registers the information on the departments of the research institution, the clerical affairs assistant (if there is one), the positions at the research institution and the researcher. IDs and passwords for the clerical affairs assistant and the researcher will then be issued.

For information on the registration procedures please refer to 10. Research Institution Procedures, 11. Research Institution Clerical Affairs Assistant Procedures and 12. Researcher Procedures in the Research Institution Clerical Affairs Assistant Manual on the e-Rad portal site (https://www.e-rad.go.jp/manual/for_organ.htm)

Please note that researcher information registered previously for the Grants-in-Aid for Scientific Research (KAKENHI) or other grant programs 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 institution shall be registered by e-Rad system operation managers upon application through the e-Rad portal site. Please refer to "How to Register (for researchers)" (https://www.e-rad.go.jp/en/researcher/index.html) for the necessary procedures.

5.3.3 Contact for inquiries regarding e-Rad operation

For inquiries regarding how to operate the e-Rad, please contact the e-Rad portal site's Help Desk. (Please refer to Chapter 14.) 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 Application Guidelines, application review status, or acceptance/rejection of applications.

5.4 Elimination of Unreasonable Duplication or Excessive Concentration of Research Funds

5.4.1 Measures to Prevent Unreasonable Duplication

With regard to the same R&D projects (of the same name and research content for which competitive research funding is allotted) by the same researchers is in a situation in which multiple competitive research funds or other research funds (subsidies, grants, joint research expenses and commissioned research funds etc. from within or outside of Japan, and all current research funds allotted to individual research conduct) is unnecessarily duplicated and allocated and any of the following apply, the R&D project in question may, according to the degree to which the above applies, the R&D project application may be rejected, the decision to adopt the R&D project may be cancelled or reduced funds may be allocated (hereinafter "non-adoption etc. of the R&D project"). It should be noted that this is not intended as a constraint upon applications for other competitive research funding programs or other research funding programs at the project application stage of this program. However, in the event that projects are adopted for other competitive research funding programs or other research funding programs, please report this promptly to the AMED division in charge of this program. In the event that there is a failure to do so it is possible that AMED may enforce non-adoption etc. of the R&D project.

(A) Applications are submitted simultaneously for multiple competitive research funding programs or other 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.

(B) Applications are repeatedly submitted of R&D projects that are essentially the same as an R&D project that has already been adopted and been allocated competitive research funds or other research funds.

(C) There is duplication regarding the use of research funds amongst multiple R&D projects.

(D) Other equivalent cases

* Not including the basic expenses and internal funds allotted by your institution of affiliation, commercial transactions stipulated by the Commercial Code or the procurement of funds through direct or indirect financing.

5.4.2 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 other competitive research funding programs or other research funding programs, in the case that the overall research funds allocated to the same 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 R&D period, and any of the following apply, AMED will enforce non-adoption etc. of the R&D project according to the degree to which the above applies.

Accordingly, in the case that a proposal document for an R&D project is submitted to and adopted by other competitive research funding programs or other research funding programs after 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 division in charge of this program. If this is not reported, there is the possibility that AMED will enforce non-adoption etc. of the R&D project.

(A) Excessive research funds are allocated in comparison to the researcher's abilities or research methods

(B) 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).

(C) Unnecessarily expensive research equipment is purchased.

(D) 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 (100%). 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.

5.4.3 Methods for the Elimination of Unreasonable Duplication or Excessive Concentration

Please submit the following information at the time of application in order that it is possible to eliminate unreasonable duplication or excessive concentration of competitive research funding, secure transparency regarding research activities, and check as to whether the appropriate amount of effort will be made.

(1) Submission of information regarding the current status of application and/or acceptance under other competitive research funding programs or other research funding programs, including other government ministry/agency programs, and regarding all current institutions of affiliations and posts held.

At the time of application, the indication on application documents and e-Rad is requested regarding information concerning the PI and Co-Investigators etc. about the current status of application and/or acceptance under other competitive research funding programs or other research funding programs, including other government ministry/agency programs (program name, research project, period of implementation, budgets sums, effort etc., hereinafter "information on research funding"), and information on all current institutions of affiliations and posts held by the PI and Co-Investigators etc. (including simultaneously held posts, participation in overseas programs for selection of senior personnel, honorary professorships without employment contracts etc., hereinafter "information on institution of affiliation and posts"). In the event that the verity of the information provided differs from that in the application forms and on e-Rad, it is possible that AMED may enforce non-adoption of the R&D project etc.

Among the information regarding research funding, with regard to information about joint research projects etc. under which confidentiality agreements etc. have been entered into, consideration will be paid on a case-by-case basis as follows in order to avoid any discouragement of industry-academia collaboration activities etc.

- It will be required to submit only the necessary information to ensure that the R&D projects applied for will not lead to any unreasonable duplication or excessive concentration of research funding, and to check that it will be possible to appropriately secure effort in the execution of R&D projects (in principle only information regarding the name of partner institutions in joint research projects, the sum of the research funding being received, and effort).
- However, in the event that it is difficult to submit information due to the content of previously concluded confidentiality agreements or there are other unavoidable circumstances that make the submission of information difficult, it is permissible to make submissions without indicating the name of other institutions or the sum of the research funding. It should be noted that even in such cases AMED may where necessary inquire with your institution of affiliation.
- In addition to institution of affiliation, information may be shared between the funding agency or relevant governmental ministries/agencies, but in such cases it will be shared among only persons obliged to maintain confidentiality.

It should be noted that when concluding confidentiality agreements in the future, applicants are requested to consider formulating the content with the prerequisite that the necessary information only may be submitted at the time of applying for competitive research funding. However, if an accord between both parties to the agreement can be reached with regard to the scope and justifiable reasons for information that should be kept secret (when it is absolutely vital for corporate strategy, and deemed to be information of particularly high confidentiality), please bear in mind that it is possible to make an agreement in which the submission of the confidential information in question is not a prerequisite.

(2) Submission of other information required in order to secure transparency regarding all of the research activities in which you are involved

In addition to information about research funding, institution of affiliation and posts held, with regard to the information necessary to secure transparency about all of the research activities you are involved in, including donations etc. and support in the form of facilities and equipment other than funds,* you will be required to pledge that you have appropriately reported this information to your institution of affiliation pursuant to all relevant rules. In the event that it is discovered that you have violated this pledge and not made appropriate reports, AMED may enforce non-adoption etc. of the R&D project.

With regard to information on the state of receipt of facilities and equipment that will not be used in the R&D project applied for but are being used in other separately pursued research, in order to avoid the unreasonable duplication or excessive concentration of competitive research funding and from the perspective of checking whether or not the R&D project can be adequately executed, in addition to making a pledge the institution of affiliation may be requested to make submissions concerning the state of ascertainment and management of such information.

*Including cases in which research facilities, equipment, devices and other goods are made available free of charge, and services provided for free.

5.4.4 Sharing 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 will be shared within the necessary extent, among the departments in charge of other competitive research funding programs, including other government ministry/agency programs, via e-Rad.

5.5 Securing Research Integrity Against New Risks Arising from the Internationalization and Promotion of Open Research in Research Activities

In order to promote Japan's science and technology and facilitate the creation of innovation in Japan, it is necessary to make the promotion of open science a fundamental principle and to vigorously support international joint research with a variety of partners in the future. At the same time, due to the new risks accompanying the internationalization and promotion of open research, in recent years there has been anxiety that the values that form the basis of the research environment such as openness and transparency will be damaged and it has been pointed out that there is a risk that researchers may unintentionally fall into a state of conflict of interest or conflict of commitment. In the midst of this state of affairs, the creation by Japan of a research environment earning international trust, while protecting the values that form the basis of the research environment, has become essential in order to promote the requisite international cooperation and international interaction.

It is therefore absolutely vital that universities and research institutions prepare rules and management systems related to conflict of interest and commitment etc., and autonomously secure soundness and fairness (research integrity) in the research activities of researchers, universities and research institutions based on the Guidelines Concerning the Securement of Research Integrity Against New Risks Arising from the Internationalization and promotion of Open Research in Research Activities (decided by the Integrated Innovation Strategy Promotion Council on April 27, 2021).

From this perspective, AMED is eliminating unreasonable duplication and excessive concentration of competitive research funding, and, while securing transparency concerning research activities, is checking whether or not it is possible to ensure the appropriate effort. In addition, with regard to the state of preparation of rules as an affiliated institution and the state of the ascertainment and management of information, AMED may inquire with the affiliated institution where necessary.

Chapter 6. Handling of Information

6.1 Handling of Information Contained in Proposal Documents

6.1.1 Purpose of Use of Information

In addition to reviewing R&D project proposals as part of the selection process, information included in proposal documents regardless of whether they are accepted or not, shall be used in analysis of research trends or macro analysis that contributes to the operation of the AMED program management, such as the creation of new programs; in the procedures regarding contracted R&D funds; for research support purposes as described in Chapter 13.

It should be noted that in order to prevent the rights and interests of the researchers submitting research proposals or their affiliated institutions from being unfairly infringed, the information in question acquired shall be used solely for the work detailed above.

In addition, with regard to the information included in proposal documents regardless of whether they are accepted or not, AMED shall manage it in line with laws and ordinances related to the management of corporate documents, protection of personal information and disclosure of information, and the AMED regulations the confidentiality of secret information included in proposal documents shall be strictly maintained to ensure that the rights and interests of the researchers submitting research proposals or the research institutions to which they are affiliated are in no way unfairly infringed. For details, please refer to the Ministry of Internal Affairs and Communications website.*

* Public records and archives management system

https://www8.cao.go.jp/chosei/koubun/index.html (in Japanese)

Act on the Protection of Personal Information, etc. (Personal Information Protection Commission (PPC))

https://www.ppc.go.jp/personalinfo/ (in Japanese)

Information disclosure system (Ministry of Internal Affairs and Communications)

https://www.soumu.go.jp/main_sosiki/gyoukan/kanri/jyohokokai/index.html (in Japanese)

6.1.2 Necessary Disclosure/Provision of Information

(A) Information related to each adopted project (program title, R&D project title, affiliated institution/position/name of people engaged in research and included in the participant list, e-Rad project/researcher/research institution number, budget amount, R&D period, research outline/abstract or Contracted R&D Result Report (public information))[1] may be sorted, classified, and made public on AMED's website, the AMED R&D projects database (AMEDfind), public databases operated by funding agencies, etc., providing cooperation under an agreement, etc., with AMED (World RePORT,[2] etc.), and other databases.

(B) 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]

(C) The 6th Science, Technology and Innovation Basic Plan (Cabinet decision of March 26, 2021) calls for thoroughness in Evidence-based Policy Making (EBPM) in science, technology and innovation administration. The information registered on e-Rad will be utilized for the appropriate evaluation of R&D

conducted with government funding, and the planning and formulation of efficient and effective comprehensive strategies, and policy on allocation of funds. 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 research funding. Information required for micro-analysis including research R&D accomplishment information and accounting report information will be provided to the Cabinet Office.

(D) 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 programs.

[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 items designated for public disclosure in the R&D Plan and the above-mentioned items shown on the Contracted Items Sheet that is to be completed if the relevant R&D 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.

Chapter 7. Points to Note between Selection and Conclusion of Agreement

7.1 Cancellation of Decision to Adopt R&D Project

The research institution implementing the R&D project must in principle, and pursuant to the stipulations of 8.1.1., conclude a contracted R&D agreement with AMED within 90 days of notification of the adoption decision (the contracted R&D agreement conclusion deadline).

The adoption of projects may be cancelled in the event that any of the following reasons for cancellation of adoption apply, even after adoption. Furthermore, in the event that despite of the existence of any of the following reasons for cancellation, they were not found out in advance and the agreement was concluded it is possible for the contract to be cancelled ex post facto.

(A) The requisite documents requested by AMED are not submitted by the contracted R&D agreement conclusion deadline.

(B) Conditions that were set for adoption of the R&D project ultimately have not been fulfilled.

(C) The R&D project does not fulfill the conditions for application.

(D) It has been discovered that during the R&D period restrictions on the application to/eligibility for participation in AMED R&D programs will be placed on researchers scheduled to participate in the R&D project in question.

(E) The planned PI or Co-Investigators of the R&D project are among persons under formal investigation for misconduct etc., and AMED does not approve their participation.

(F) In addition to the above, when it is not possible to conclude the agreement before the R&D agreement conclusion deadline due to reasons attributable to the research institution implementing the R&D project (including the event that there are violations of Representation and Warranty and matters to be observed as stipulated in the agreement).

7.2 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 institution to have carried out misconduct in accordance with Japanese Government guidelines for responding to misconduct[1] 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, etc. implemented by the national government or independent administrative agencies based on the findings of the research institution, or whose period of restriction on application to/eligibility for participation in competitive research funding programs, etc. implemented by the national government or independent administrative agencies has ended).[2]

(B) In the case that persons who are the subject of a formal investigation (hereinafter referred to as the "formal investigation") being conducted by the research institution 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 institution in question and either the PI or Co-Investigator (if there is a subcontractor, including the Co-Investigator or equivalent person affiliated with the subcontractor) for the R&D Plan, AMED has been notified of the relevant target person 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 person(s).

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

[1] 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.

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

7.3 Preparations for Concluding Agreement

Following the adoption of an R&D project, the research institution implementing the R&D project shall be required to prepare the following (A) to (C) in order to enable procedures for concluding the contracted R&D agreement with AMED to proceed quickly and smoothly. Documents required for the agreement (plan forms etc.) shall be provided separately after projects have been adopted.

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 (Please note that some parts of the R&D Plan may be required to be submitted in English.).

(A) Prepare an Overall R&D Plan, R&D Plan and other documents required for the agreement

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

(C) Organize accounting regulations, contracted research regulations, and rules for employee inventions, etc.

7.4 Submission of Data Management Plans (DMPs)

With regard to awarded projects, the PI is requested to submit* a DMP to AMED when they conclude a contracted R&D agreement after adoption. Successful applicants will be separately informed regarding the requisite documents (forms) after adoption.

* The data etc. arising from R&D programs using public funds are a form of assets of the general public, and one of AMED's roles is to ascertain the location of data that is currently unknown, collect it, secure its quality, assess its significance, store and use it in an appropriate and fair manner.
* By ascertaining the types of R&D data, where they are stored, the person in charge of managing the data, the data usage and sharing plan policy, and the location of the human resources related to the data through DMPs, AMED seeks to strengthen its management and catalytic functions, and to the greatest extent possible be of use in encouraging collaboration between different R&D projects, and avoiding duplicated R&D.
* The DMP is a document recording what sort of data arises from what R&D project and who is managing it.
* It is requested that DMPs 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.
* Please complete the DMP in strict accordance with the Guidelines on AMED Research Data Utilization and the Guide for Completing DMPs. (The Guidelines on AMED Research Data Utilization explain the obligation of submitting DMPs, and functions and role etc. of the plans, so please refer to them.)
* With regard to the DMP content that can be made public or information that the content is statistically processed these may be made public along with other project information. Please refer to Chapter 10 for details of the utilization of DMP.
* Please refer to the following for further details.
https://www.amed.go.jp/koubo/datamanagement.html (in Japanese)

7.5 Submission of Research and Development Tag Information Sheets

Using R&D tags, AMED will comprehensively and chronologically ascertain the research purpose, nature of research, research modality, developmental phase, target disease (ICD10), disease area (seven fields) and noteworthy matters etc. of R&D projects regarding integrated projects and disease areas. By ascertaining these, AMED will make visible the entire scope of projects, strengthen management competence and catalytic abilities, encourage collaboration in different R&D projects and put them to use in the formulation of future call documents. Therefore, with regard to adopted projects, the PI is requested to submit* R&D tags to AMED when concluding the contracted R&D agreement after adoption and also when applying for grants for subsidized projects. Separate notification concerning the requisite documents (forms) will be made after adoption.

* R&D tags are used to organize the details of each R&D project—the purpose and nature of the R&D and what phase it is at—by target disease and disease area, and serve to enable the vertical and horizontal ascertainment of AMED projects from an integrated project (horizontal) and disease area (vertical) perspective.

*Please use an Excel table to select the R&D tags for research purpose, nature of research, research modality, developmental phase, target disease (ICD10), disease area (seven fields) and noteworthy matters etc.

* Please strictly observe the writing guidelines for R&D tags.
* With regard to information of a publishable content consisting of parts of the R&D tag items and information recorded that have been statistically processed, this may be published in conjunction with other project information.

Chapter 8. Conclusion of Contracted R&D Agreements

8.1 Conclusion of Contracted R&D Agreements

8.1.1 Agreement Conditions

With regard to awarded R&D projects, a contracted R&D agreement must be concluded between the research institution implementing the R&D project and AMED. The research institution implementing the R&D project becomes able, through the conclusion of an agreement, to receive contracted R&D funds from AMED and implement the adopted R&D project. The contracted R&D agreements are single-year agreements in accordance with the principles of the accounting period of the national government. AMED will provide successful applicants with details of the documents required for the agreement and the procedures after adoption.

The contracted R&D agreements shall, in principle, be concluded within 90 days of notification of adoption (the contracted R&D agreement conclusion deadline). As stated above in 7.1 above, in the event that the required documents are not submitted prior to the contracted R&D agreement conclusion deadline, or the conditions decided at the time the R&D project was adopted have not been fulfilled based on the opinions of the Project Evaluation Panel, PS, PO, etc., take adequate care as the agreement cannot be concluded even if it is for an adopted R&D project, and the adoption decision may be rescinded.

Even after the contracted R&D agreement has been concluded, in the case that unavoidable circumstances arise due to budget restrictions, the R&D plan may be revised or suspended (including early conclusion of projects due to achievement of R&D plans).

The PS, 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.

It should be noted that, 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 test and research institutions run by local government), only in the case that the relevant institution or the PI or Co-Investigator affiliated with the relevant institution makes a request based on reasonable grounds and following discussion with AMED shall a payment method of the R&D grant being paid by AMED to the PI or Co-Investigator of the relevant institution be adopted. (In such cases, payment will be in accordance with the Guidelines for Handling of R&D Grants prescribed by AMED.) If this is the case, administration related to R&D grant accounting shall be entrusted to the head of the relevant institution. Furthermore, in the case that the need to carry out the research content at the Principal Institution and the Subsidiary Institution in an integrated manner under the R&D plan is recognized and the Subsidiary Institution is not a national facility or other institution, approval may be given under this program for the R&D to be subcontracted. However, even in the case that the R&D is subcontracted, as a general rule project accounting shall be performed by the subcontractor and the subcontractor shall be required to undergo government inspection and auditing by AMED in response to requests from AMED.

8.1.2 Administrative Procedures Regarding Conclusion of Agreements

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

*https://www.amed.go.jp/keiri/index.html (in Japanese)

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

8.1.4 Determination of Contracted R&D Funding Amount

Contracted R&D funding amounts are determined based on examination of the Contracted R&D Accomplishments Report which is required to be submitted in accordance with the Contracted R&D Agreement following the conclusion of the contracted R&D agreement period for the relevant fiscal year. During this examination, in the case that expenditure for research purposes is found to have been used fraudulently or for purposes not recognized as contracted R&D activities under the Contracted R&D Agreement, all or part of the expenditure may be required to be returned. Furthermore, the person(s) conducting the research who used the funds fraudulently may be excluded from any agreements with AMED for a certain period of time, depending on the extent of the fraud. For details, please refer to Chapter 12.

8.2 Scope and Payment of Contracted R&D Funds

8.2.1 Scope of Contracted R&D Funds

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

Currently, improvements regarding the systems for competitive research funds are being promoted, with the 6th Science, Technology, and Innovation Basic Plan, the Integrated Innovation Strategy 2022 and the Comprehensive Package for Research Competitiveness Enhancement and Young Researcher Support. Based on this, under this program the direct costs can cover personnel costs for PIs and Co-Investigators as well as expenses for entrusting other persons with PIs' work other than research and development ordinarily performed by PIs at their affiliated institutions (buyout expenses). (Although no ceiling is set for the amount spent on buyout costs in the case of AMED-CREST, there is a two million-yen ceiling for these amounts in the case of PRIME.)

	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, 3] 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 accomplishments 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, expenses for entrusting other persons with PIs' work other than research and development ordinarily performed by PIs at their affiliated institutions (buyout expenses), [3] amount equivalent to consumption tax related to untaxed transactions, etc.
Indirect costs[4, 5]	Expenditure used by research institutions as necessary costs for managing the research institutions 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] https://www.amed.go.jp/keiri/index.html (in Japanese)

[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 at the time of application, your personnel costs are paid from external funds that you have been awarded.

[3] With regard to the requisite conditions and details of procedures in the event of disbursing personnel costs and buyout expenses for PIs and Co-Investigators, please refer to the Administration Manuals and Forms[1] in the Program Administrative Procedures (Forms and other documents) section of the AMED website.

[4] Indirect costs are allocated when AMED concludes a contracted R&D agreement with a national university corporation, inter-university research institute corporation, independent administrative agencies, special corporation, general incorporated association, general incorporated foundation, public interest incorporated association, public interest incorporated foundation, private enterprise, or private university, etc. The fixed percentage will not exceed 30%. With regard to Subsidiary Institutions (excluding researchers affiliated with national facilities or other institutions) also, indirect costs are allocated in accordance with direct costs.

[5] In cases in which the indirect subsidies payment method is used with regard to researchers affiliated to a national facility or other institution (excluding the National Institute for Educational Policy Research) they become ineligible for allocation of indirect costs.

8.2.2 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."[1]

Note 1: 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 clinical 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 institution has created a system for registering cases for clinical trials/clinical studies 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 institution can request case registration from other medical institutions in a kind of outsourcing method. For more details please refer to the section entitled "Management of medical institution expenses for investigator-initiated trials or clinical studies," which can be found on the AMED website under "Management of research expenses."[2] Facilities where there is a sufficient administrative support system for clinical trials/clinical studies may continue using their current management method for the foreseeable future.

Note 2: In place of the supercomputer joint use service that will be taken out of service in FY2021, it will be possible to use the supercomputers prepared by the Biobank–Construction and Utilization biobank for genomic medicine Realization (B-Cure) (Platform Program for Promotion of Genome Medicine/Large-scale Genome Analysis Infrastructure Project) for certain purposes and under certain conditions. For more details please consult the Division of Genomic Medicine secretariat at this email address: genome-supercom"AT"amed.go.jp (Change "AT" to @ when inputting the address.)

[1] https://www.amed.go.jp/keiri/index.html (in Japanese)

[2] https://www.amed.go.jp/program/kenkyu_unyo.html (in Japanese)

8.2.3 Encouragement of Shared Use of Facilities and 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." *

* https://www.amed.go.jp/keiri/index.html (in Japanese)

8.2.4 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.

8.2.5 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."*

* https://www.amed.go.jp/keiri/index.html (in Japanese)

8.2.6 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 research fund" (revised on October 1, 2021 at the Liaison Meeting of Relevant Ministries on Competitive Research 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."*

* https://www.amed.go.jp/keiri/index.html (in Japanese)

8.2.7 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 in implementing preliminary surveys or deciding 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."*

*https://www.amed.go.jp/keiri/index.html (in Japanese)

8.3 Handling of Acquired Goods

8.3.1 Ownership of Acquired Goods

Ownership of goods, etc. acquired by Universities, etc.,[1] through direct costs (hereinafter referred to as "Acquired Goods") shall revert[2] to the Universities, 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 useful 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. Companies, etc. shall, throughout the contracted R&D period, manage the relevant acquired goods properly with the due diligence of a prudent manager.

[1] "Universities, etc." include:

a. Incorporated educational institutions such as national university corporations, public university corporations, and private universities
b. Public research institutions such as national research institutions, public test and research institutions run by local government, and independent administrative agencies
c. Organizations with a public nature, such as public interest corporations, that are recognized by AMED

[2] "Companies, etc." is a general term for research institutions other than "Universities, etc."

8.3.2 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 useful life* and the tangible property may be transferred to the Companies etc., for a fee upon the evaluation of AMED after its useful 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 duration of useful life shall be the number of years stipulated in Appended Table 6 “Useful Life Table of Depreciable Assets for R&D of the Ministerial Order on Useful Life of Depreciable Assets” (Ministry of Finance Order No. 15 of 1965). (Four years for tools, appliances and equipment.)

8.3.3 Disposal of Radioactive Waste

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

Chapter 9. Progress Management of Awarded R&D Projects

9.1 Progress Management of Projects

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 management actions of the R&D Area taken by the PS and PO, the results of project evaluations, the budget conditions of the overall program, and so on.

In all awarded projects, the PS, PO, etc. shall manage progress of their projects. In doing so, important research data (including experiments) on which the R&D project proposal is based may be verified from the perspective of progress management, even if the relevant research was conducted prior to conclusion of the contracted R&D agreement.

A Contracted R&D Result Report, serving as an appendix to the Contracted R&D Accomplishments Report, is required to be submitted each fiscal year for all awarded R&D projects according to the contracted R&D agreement.

It should be noted that 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 also note that, upon referral to the R&D Plan and depending on the progress status, review of the project plan or cancelation (early conclusion) of the project may be carried out.

In addition, R&D projects moving into the practical application stage (R&D projects that are within the target scope of the regulatory science strategy consultation or other PMDA consultation services), are, as a condition of adoption, required to implement each clinical trial according to the research plan agreed in advance at the Regulatory Science Strategy Consultation or other consultation services (face-to-face advice) provided by the Pharmaceuticals and Medical Devices Agency (PMDA). Furthermore, based on appropriate information management, the research institution shall consent to AMED attending various kinds of consultation interviews under the Regulatory Science Strategy Consultation program etc. during the R&D period and share face-to-face advice records and related information with AMED.

For research* undertaking clinical trials or clinical studies with a view to creating innovative drugs, medical devices etc., or nonclinical studies aimed at conducting such trials/studies during the R&D period, research institutions 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 research that is not aimed at developing new drugs or medical devices, etc. or that differs from normal processes for evaluating/approving new medical technology.

9.2 Mid-term Review, Ex-Post Evaluations etc.

Under this program, awarded projects whose planned R&D period is more than four years 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. Awarded projects whose planned R&D period is four years or less 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, projects under this program shall undergo a Mid-term Review, regardless of the timing.

Based on evaluation results, AMED may cancel (conclude early) a project in accordance with the overall decision of the PS, PO, etc.

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

9.3 Presentations at Accomplishments Report Meeting

As part of accomplishments 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.

Chapter 10. Handling of R&D Accomplishments

With regard to the handling of R&D accomplishments, research institutions are obligated under contracted R&D agreements to strictly comply with items regarding R&D accomplishment reporting, intellectual property (IP) and usage of R&D accomplishments.

10.1 Inclusion of Systematically Assigned Numbers in the Acknowledgement Section of Papers

When publicizing the R&D accomplishments made under this program, please be sure to state that the accomplishments are due to AMED support and include the grant number for acknowledgements in the acknowledgements section. For more details please check the AMED "Administration Manual for Contracted R&D Agreements."*

* https://www.amed.go.jp/keiri/index.html (in Japanese)

10.2 Submission and Publication of Contracted R&D Result Reports and DMP (the Latest Version upon Conclusion of R&D)

Research institutions shall submit a Contracted R&D Result Report that summarizes the research accomplishments of the R&D project, serving as an appendix to the Contracted R&D Accomplishments Report, and a DMP (the latest version upon conclusion of R&D). Please note that the deadline for submission of the report is within 61 days from the end of the term of the contracted R&D agreement or from the conclusion/cancellation/discontinuance of the contracted R&D, whichever comes first. In the case that the Contracted R&D Result 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. It should be noted that some parts of the Contracted R&D Result Report may be required to be submitted in English.

A part of the items in the Contracted R&D Result 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 report form with regard to information prior to patent applications, unpublished information about the details of patents being applied for, knowhow and other confidential sales information and any other undisclosed information.

Moreover, with regard to final Result Reports produced at the end of R&D projects that have lasted for several years, the content under the section of "Items for Disclosure" in the report compiled by the PI upon Ex-Post Evaluation will be published at appropriate times on the AMED website.

Furthermore, from the perspective of the use of R&D data through data sharing, with the objective of introducing R&D data generated, acquired or collected in connection with R&D supported (contracted or assisted) by AMED to universities, companies and other research institutions that are considering its use, AMED plans to publish on its website the parts that it is possible to make public of the DMP (the latest version upon conclusion of R&D project). The undisclosed data will be appropriately managed by AMED, and in some cases AMED might, where necessary, make enquiries to PIs in order to confirm details.

10.3 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 research institutions under the condition that the requirements provided for in Article 17 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 research institutions so that the accomplishments of these R&D activities can be used efficiently in business activities. Under this program, it is expected that research institutions 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. Furthermore, please consult with AMED in advance in the event that R&D accomplishments or intellectual property rights relating to R&D accomplishments are succeeded from a domestic subsidiary to an overseas parent company.

10.4 Measures towards the Practical Application of R&D Accomplishments

Research institutions 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 Intellectual Property Policy* ensuring that appropriate measures have been implemented within the research institution'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 Division of Intellectual Property, Department of Intellectual Property and Technology Transfer, provides consistent support for maximizing and achieving the practical application of R&D accomplishments that have reverted to the research institutions, so do not hesitate to contact the Medical IP Desk (For details, please refer to Chapter 13).

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

10.5 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 research institutions. Researchers are strongly recommended to peruse these IP educational materials prior to carrying out research.

* https://www.amed.go.jp/chitekizaisan/chizai_kyouzai.html (in Japanese)

10.6 Securing Open Access to R&D Accomplishments

Having secured the necessary IP rights, research institutions are requested to cooperate in ensuring open access to research accomplishments (including data etc. acquired) as far as possible.

10.7 Handling of Data

With regard to the data created, obtained or collected in connection with R&D supported (contracted or assisted) by AMED, or data (R&D data) produced through the processing etc. of data as a result of a contracted R&D agreement

in which AMED is the assignor, please treat it in pursuance with the Contracted R&D Agreements, the AMED Basic Policy on Handling of R&D Data and the Guidelines on AMED Research Data Utilization.*

* https://www.amed.go.jp/koubo/datamanagement.html (in Japanese)

Chapter 11. Obligations of Research Institutions and Researchers in Implementing this Program

11.1 Compliance with Laws and Ordinances

In implementing this program, research institutions 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 institutions 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.

a. Fabrication: creation of data or research accomplishments that do not exist.

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

c. 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 researcher 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.

11.2 Management Responsibility for Executing Contracted R&D Funds

The contracted R&D funds shall be executed by the research institution in accordance with the contracted R&D agreement. For this reason, research institutions shall abide by the principles stipulated under "Competitive research funding, etc. should be managed at the responsibility of the research institution," and research funds shall be managed under the responsibility of research institutions. Moreover, 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.

11.3 Participation in/Completion of Responsible Conduct of Research (RCR) Education Program

As part of measures to prevent misconduct from occurring, AMED requires all researchers participating in this program to take and complete a responsible conduct of research (RCR) education program. Accordingly, research institutions shall implement RCR education for researchers and report to AMED on the status of participation. Please

note that in the case that a researcher does not complete a RCR education program, execution of contracted R&D funds may be suspended until completion of the RCR education program is confirmed.

11.3.1 Persons Required to Participate in RCR Education Program/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 RCR education using one of following programs/materials.

• A Casebook for Responsible Research Conduct (AMED) (in Japanese)
• Compilation of Near Incidents regarding Research Integrity (AMED) (in Japanese)
• APRIN e-Learning Program (eAPRIN) (in Japanese)
• "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") (in Japanese)
• Programs implemented by research institutions whose content is deemed to be equivalent to the that of the above programs

Furthermore, the Clinical Trials 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.

i) Training conducted by a Clinical Research Core Hospital for persons working in the clinical research field.*
ii) 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 ii), but it is essential that the "Kenkyusekinin Ishi" (Principal Investigator) undergoes thorough training and understands the training content.

* With regard to planned training schedules conducted by a Clinical Research Core Hospital, please check the section "Regarding Clinical Research Core Hospitals" on the website below.

https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/chiken.html (in Japanese)

11.3.2 Period to Participate in RCR Education Program

As a general rule, persons required to participate in the RCR education program are requested to endeavor to do so prior to the conclusion of the agreement for the initial fiscal year of the R&D project, and should continue to participate in the RCR education program as appropriate thereafter. (Previous participation in the RCR education program may also be valid.)

11.3.3 Role of Research Institutions and Reporting Status of Participation in RCR Education Program

Research institutions shall ensure that persons required to participate in the RCR education program as listed above who are affiliated with their institution (included a subcontractor) undergo RCR education using one of the programs/materials listed above; compile information on researchers' RCR education status; and submit a report on the status of participation on the form prescribed by AMED by e-mail to AMED (Division of Research Integrity, Social Co-Creation and Legal Affairs, Department of Research Integrity and Project Management). (Seal need not be affixed.)

For information regarding where and how to submit reports, please check "The Responsible Conduct of Research (RCR) Education Program" page under "Research Integrity" on the AMED website below.

• Subjects of report	PIs and Co-Investigators among the persons required to undergo research ethics training in programs commencing in/after FY2023
• Deadline for submission	By the end of the last day of the month following the date of conclusion of the agreement in the first fiscal year of the R&D project
• Documents to be submitted	Report on the Status of Participation in RCR Education Programs (Please download the form from the AMED website)
• URL	https://www.amed.go.jp/kenkyu_kousei/kyoiku_program.html (in Japanese)

11.4 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 Trials 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 institutions 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 institution to improve the situation or suspend provision of R&D funds, as well as require the research institution to return all or part of the R&D funds already paid.

11.4.1 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 are the target persons. 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.

11.4.2 Conflict of Interest Management in Accordance with Article 21 of the Ordinance for Enforcement of the Clinical Trials Act

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

11.4.3 Submission of Reports on the State of COI Management

Each research institution, etc. should prepare a Report on the State of COI Management, and submit it to AMED within 61 days after the end of each fiscal year or the conclusion of the contracted R&D project. The Reports on the State of COI Management are to be posted on the AMEDfind database.*

Information including the forms of the Report on the State of COI Management, 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.*

* For details regarding conflict of interest management, please refer to the AMED website below.

- 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 (in Japanese)

11.5 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 institutions 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 institutions concerning related laws/ordinances and policies as an item related to the Contracted R&D Result Report, which is an appendix to 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 amendment of laws/ordinances, etc.

- Act on Regulation of Human Cloning Techniques (Act No. 146 of 2000)
- Act on the Prevention of Infectious Diseases and Medical Care for Patients Suffering from Infectious Diseases (Act No. 114 of 1998; partially revised on February 3, 2021)
- Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003)
- Act on Securing Safety of Regenerative Medicine (Act No. 85 of 2013; revised on December 14, 2018)
- Clinical Trials Act (Act No. 16 of 2017)
- Ordinance for Enforcement of the Clinical Trials Act (Ordinance of the Ministry of Health, Labour and Welfare (MHLW) No. 17 of 2018)
- Ministerial Ordinance on Good Clinical Practice for Drugs (Ordinance of the Ministry of Health and Welfare No. 28 of 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)
- Guidelines on the Handling of Specified Embryos (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) No. 31 of 2019; partially revised on June 30, 2021)
- 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. 4 of 2019; partially revised on March 31, 2022)
- Guidelines on the Utilization of Human Embryonic Stem Cells (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) No. 68 of 2019; partially revised on March 31, 2022)
- Guidelines for the Distributing institute of Human Embryonic Stem Cells (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) No. 69 of 2019; partially revised on March 31, 2022)

○ 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; partially revised on March 31, 2022)

○ 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; partially revised on March 31, 2022)

○ Ethical Guidelines for Research Using Gene Modification Techniques on 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. 3 of 2019; partially revised on March 31, 2022)

○ 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 Life Science and Medical/Health Research Involving Human Subjects (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 2021; partially revised on March 10, 2022)

○ Policies on Clinical Research Involving Gene Therapy (Public Notice of the Ministry of Health, Labour and Welfare (MHLW) No. 344 of 2015; partially revised on March 25, 2022)

○ 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; partially revised on April 28, 2021)

* Please refer to the following websites for details regarding bioethics and ensuring safety.

- MEXT's Life Sciences Forum "Initiative on Bioethics and Biosafety"
  https://www.lifescience.mext.go.jp/bioethics/index.html (in Japanese)
- Regarding Guidelines on Research (Ministry of Health, Labour and Welfare (MHLW))
  https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/hokabunya/kenkyujigyou/i-kenkyu/index.html (in Japanese)

11.6 Obligation to Take Action with Regard to System Maintenance, etc.

11.6.1 Obligation to Take Action with Regard to System Maintenance

All research institutions must strictly comply with the items required to be implemented by research institutions 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) 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 1, 2021).

* Please refer to the following websites for details of each guideline.

- Guidelines for Responding to Misconduct in Research
  https://www.mext.go.jp/a_menu/jinzai/fusei/__icsFiles/afieldfile/2015/07/13/1359618_01.pdf
- Guidelines for Management and Audit of Public Research Funds at Research Institutions (implementation standards)
  https://www.mext.go.jp/a_menu/kansa/houkoku/1343904_21.htm (in Japanese)

11.6.2 Confirmation of System Maintenance

In concluding the agreement for this 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. (Concluding the agreement will not be permitted without the submission of this checklist.)

Having checked the various websites, all research institutions are requested to download the 2023 edition of the checklist format, complete the requisite items, and submit (upload) the checklists to the Ministry of Education, Culture, Sports, Science & Technology using e-Rad by concluding the agreement.

It should be noted that with regard to research institutions submitting the 2022 edition of the checklist, concluding the agreement will be permitted, but in such cases institutions are requested to submit the 2023 edition of the checklist A by December 1, 2023, and checklist B by September 30, 2023.

(A) Self-evaluation (Including System Maintenance) Checklist	
• Basis	Guidelines for Management and Audit of Public Research Funds at Research Institutions (implementation standards)
• Submit to	Office of Competitive Research Funding Administration, Research and Development Infrastructure Division, Science and Technology Policy Bureau, MEXT
(B) Checklist of research misconduct	
• Basis	Guidelines for Responding to Misconduct in Research
• Submit to	Office for Research Integrity Promotion, Research and Development Infrastructure Division, Science and Technology Policy Bureau, MEXT

Note: With regard to how to submit the FY2023 checklists, please check the websites of e-Rad or the Ministry of Education, Culture, Sports, Science and Technology (MEXT).

11.6.3 Necessity of Submitting a Checklist

With regards to the checklists (A) and (B) cited above in 11.6.2, in the case that applicants have already submitted a checklist the relevant 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.

However, both of these checklists are required to be submitted on an annual basis, so research institutions that are continuing implementation in the following year and beyond must also submit the checklists to MEXT once each fiscal year.

Furthermore, with regard to the checklist (A) above, institutions that are not allocated by the competitive research funding, etc. of MEXT or independent administrative agencies under MEXT are not required to submit the checklist. With regard to checklist (B), submission is not required by institutions other than those that are allocated a budget by MEXT or the independent administrative agencies under MEXT and conduct research activities.

* 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 institutions 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 web page on How to Register (for research institutions) on the e-Rad portal site detailed below.

https://www.e-rad.go.jp/organ/index.html (in Japanese)

11.6.4 Cooperation with Surveys

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

11.6.5 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 institution'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 institution it may become subject to measures such as reducing the indirect costs with regard to all competitive research funding allocated by MEXT and independent administrative agencies under the jurisdiction of MEXT.

Chapter 12. Countermeasures to Misconduct, Fraudulent Use, and Fraudulent Receipt

12.1 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 institution in relation to this program (if there is a subcontractor, including in cases that researchers or others at the subcontractor engaged in this program are suspected to have committed Misconduct, etc. in in this program), the research institution 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 (decided by the Minister of Education, Culture, Sports, Science and Technology on August 26, 2014); 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 1, 2021); and AMED Regulations for Responding to Misconduct in Research Activities.

In the event that it is deemed necessary for the research institution to conduct a formal 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 accused and/or the research institution to suspend use of research funds under this program as a temporary measure during the formal investigation if necessary.

Furthermore, the research institution 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. For details regarding items that should be incorporated into the final report, please refer to the Guidelines for Responding to Misconduct in Research (decided by the Minister of Education, Culture, Sports, Science and Technology on August 26, 2014); 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 1, 2021); and 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 institution 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 institution 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 institution extends the deadline for submission of the final report, AMED may take measures against the research institution such as reducing indirect costs by a certain percentage or suspending execution of contracted R&D funds.

12.2 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 institution 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); 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 1, 2021); and AMED Regulations for Responding to Misconduct in Research Activities.

12.2.1 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 institution and demand the return of all or part of the contracted R&D funds from the research institution. In the event that contracted R&D funds are returned, the relevant research institution 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 institution for the next fiscal year or thereafter.

12.2.2 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 placed on the researcher's application to and eligibility for participation in AMED programs, the related government ministries and agencies will be informed of an outline of the misconduct in question (name of the researcher responsible for misconduct, program name, research institution, R&D project, budget amount, fiscal year of research, details of the misconduct and details of measures taken against them etc.). In this way, their application to and eligibility for participation in competitive research funding programs provided by related government ministries/agencies may similarly be restricted in some cases.

- 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		10 years

<table>
<tr><td rowspan="5">Misconduct</td><td colspan="2">from the outset of the research</td><td></td><td></td></tr>
<tr><td rowspan="3">2. Author of academic paper, etc. related to research in which there has been misconduct</td><td rowspan="2">The author responsible for the academic paper in question (supervisor, first author, or other position of responsibility deemed equivalent)</td><td>The impact on the advancement of research in the relevant field or society is large, and the maliciousness of the misconduct is deemed to be high.</td><td>5–7 years</td></tr>
<tr><td>The impact on the advancement of research in the relevant field or society is small, and the maliciousness of the misconduct is deemed to be low.</td><td>3–5 years</td></tr>
<tr><td>Author other than that listed above</td><td></td><td>2–3 years</td></tr>
<tr><td colspan="2">3. An individual involved in misconduct other than that stipulated in 1 or 2</td><td></td><td>2–3 years</td></tr>
<tr><td colspan="2" 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.

Details of fraudulent use/fraudulent receipt	Period of application/eligibility restriction
1. The severity of the fraudulent use of competitive funds will have a limited impact on society and the maliciousness of the actions is deemed as being low	1 year
2. The severity of the fraudulent use of competitive funds will have a major impact on society and the maliciousness of the actions is deemed as being high	5 years
3. Cases other than 1 and 2 and the period of application/eligibility restriction will be judged based on an impact on society and the maliciousness of the actions	2–4 years
4. In the event of personal diversion of funds for private benefit regardless of 1-3 above	10 years
5. In the event that a project is selected for research activities as the result of deceit or other fraudulent methods	5 years
6. In the event that a person or persons are not directly involved in fraudulent use of research funds but use the research funds in a manner infringing 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 to 4, the researcher's actions will have a small social impact and their maliciousness is deemed as being low, and the funding amount used fraudulently is small.
- In 6, the researcher's actions will have a small social impact and their maliciousness is deemed as being low.

Note 2: With regard to 6 above, periods will be decided upon with due consideration of the severity of infringement of diligence by the researcher with duty of diligence.

12.2.3 Restrictions on Researchers Whose Application to and Eligibility for Participation in Other Competitive Research Funding Programs etc. Has Been Restricted

With regard to researchers who have been found to have carried out misconduct under research funding programs (including but not limited to competitive research funds, etc. and management expenses grants) (including programs for which new applications are solicited in FY2023 or later, and programs completed in or before FY2022) other than this program, which are under the jurisdiction of the national government or an independent administrative agency 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 as PI or Co-Investigator 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 this program becomes known after the conclusion of the contracted R&D agreement, the relevant agreement may be cancelled.

12.2.4 Cases in Which it is Suspected that Misconduct Has Occurred Under Another Competitive Research Funding Program

In the case that there is a complaint, etc., that a researcher, etc. participating in this program is suspected of perpetrating misconduct under another competitive research funding program (including completed programs), the research institution with which the relevant researcher, etc. (if there is a subcontractor, including researchers or others at the subcontractor engaged in this program) is affiliated is obligated to report to AMED that a formal 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 institution to which the relevant researcher is affiliated fails to make the above report, the contracted R&D agreement may be cancelled.

12.2.5 Disclosure of Misconduct

In the case that the measures and/or restrictions prescribed in 12.2.1 and 12.2.2 above are implemented under this program, an outline of the misconduct in question (program name, research institution, fiscal year of research, details of the misconduct and details of measures taken against them) 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); 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 1, 2021); and AMED Regulations for Responding to Misconduct in Research Activities. In addition, the misconduct may be similarly disclosed by the related government ministries/agencies.

Furthermore, as both MEXT guidelines state that when misconduct is identified the research institution must swiftly publicize the results of its findings all institutions 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.*

* https://www.mext.go.jp/a_menu/jinzai/fusei/1360483.htm (in Japanese)
https://www.mext.go.jp/a_menu/kansa/houkoku/1364929.htm (in Japanese)

12.3 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 FY 2017 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*:

The officers in charge of responsible conduct of research (RCR) education and the officers in charge of promoting compliance (hereinafter 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 RCR 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.

* https://www.amed.go.jp/kenkyu_kousei/rionetwork.html (in Japanese)

Chapter 13. 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 may be requested that details of these efforts be included in Contracted R&D Result Reports.

13.1 Promotion of Social Co-Creation in Medical R&D

As an initiative in Social Co-Creation, AMED promotes on an organizational basis: 1) responses to ethical, legal and social issues (ELSI) arising from medical R&D; 2) diversity to achieve diverse well-being; and 3) addressing sustainable development goals (SDGs) for medical R&D in Society 5.0.

Reference: AMED website "Social Co-Creation"
https://www.amed.go.jp/socialcocreation/index.html (in Japanese)

13.1.1 Promotion of Dialogue and Cooperation with Society

According to the "Promotion of Dialogue on Science and Technology with the Public (a Basic Approach Policy)" (June 19, 2010, decision of the Minister of State for Science and Technology Policy and expert members of the Council for Science and Technology Policy), in order to constantly produce excellent accomplishments in science and technology and further develop science and technology in Japan it is considered essential to adopt a stance of returning accomplishments in science and technology to the public, obtaining the understanding and support of the public, and jointly promoting science and technology. In the event of adoption in this round of solicitation, efforts to explain the content and accomplishments of research activities to society and the public in easily understood terms, and efforts to promote dialogue and cooperation among various stakeholders are necessary. Based on this, we ask that program participants make active efforts in connection with "Dialogue on Science and Technology with the Public," including holding public lectures and symposiums on research accomplishments, continuously posting information on research accomplishments on the internet, and holding roundtable meetings with various stakeholders.

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

13.1.2 Promotion of the Patient and Public Involvement (PPI) in Medical Research/Clinical Studies

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 accomplishments 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. Researchers are expected to proactively incorporate the knowledge and opinions of patients and members of the general public in the process of medical research/clinical trials, as addressing this initiative is expected to generate research accomplishments that will be more beneficial to patients and others, lead to smoother implementation of

research and improve protection of clinical trial subjects. For these reasons, AMED requests that program participants proactively incorporate PPI into medical research and clinical studies.

Reference: AMED website "Patient and Public Involvement (PPI)"
https://www.amed.go.jp/ppi/index.html (in Japanese)

13.2 Health Risk Information

In accordance with requests from the Ministry of Health, Labour and Welfare, AMED requires researchers to report information obtained in the process of conducting research that could seriously threaten the lives and/health of members of the general public (hereinafter referred to as "Health risk Information") to the Ministry of Health, Labour and Welfare using the prescribed form.[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] https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/kenkoukiken.doc (in Japanese)

[2] https://www.amed.go.jp/keiri/index.html (in Japanese)

13.3 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.

13.4 Measures Related to the IP Strategic Program

The Intellectual Property 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. As the Intellectual Property Strategic Program 2014 (Intellectual Property Strategy Headquarters on July 4, 2014),[1] sets forth the strategic utilization of certification in order to further invigorate international standardization activities, AMED is also to promote R&D with a view to international standardization/certification.

Accordingly, in the case that a public research institution under this program carries out R&D with the potential to lead to international standardization/certification, the research institution 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] Excerpted from the Intellectual Property Strategic Program 2014
https://www.kantei.go.jp/jp/singi/titeki2/kettei/chizaikeikaku20140704.pdf (in Japanese)
First pillar: Building up a global intellectual property 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

13.5 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 and AMED IP Liaisons[1] covering IP strategy and out-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 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 (Contact point for medical IP consultation). 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 (in Japanese)

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

13.6 Seeds/Needs Matching Support System "AMED ぷらっと®/AMEDplat"

In April 2018, AMED launched the "AMED ぷらっと®/AMEDplat" 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 accomplishments in the medical field. This enables research seeds to be showcased to staff in charge of in-licensing at companies, facilitating university-company collaboration at an early stage. In order to achieve this it is requested that you proactively register research seeds in the medical field in the AMED ぷらっと® /AMEDplat system. Note that you should refer to the AMED ぷらっと® /AMEDplat website* regarding details about the launch of use of the AMED ぷらっと® /AMEDplat.

* AMED ぷらっと® /AMEDplat website:

https://www.amed.go.jp/chitekizaisan/amed_plat.html (in Japanese)

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

In order to link the accomplishments of outstanding basic research by universities, etc. to the practical application of drugs, AMED's Department of Innovative Drug Discovery and Development (hereinafter referred to as the "iD3") 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 out-licensing to a company.

The iD3 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 out-licensing to drug companies; provides technological support for applied research (exploratory study, optimization study, etc.) and nonclinical studies (conforming to GLP (Good Laboratory Practice)); provides introduction and contracted support of CROs (Contract Research Organizations) and CMOs (Contract Manufacturing Organizations), etc.; and facilitates out-licensing process to drug companies.

In this way, the iD3 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 out-licensing to drug companies. For this reason, R&D projects that are related to drug development may receive active support from the iD3 in coordination with the division in charge of this program.

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 6.). Furthermore, the iD3 provides the above-mentioned support based on requests by researchers.

In the same way, with regards to the applied R&D projects related to drug development that is or was supported by the iD3, AMED provides the information on the support content to the division in charge of this program.

Please refer to Chapter 14 for references related to support provided by the AMED Drug Discovery Support Network and the iD3.

13.8 Support for Research Seeds and R&D through Translational and Clinical Research Core Centers

AMED is building a system to consistently link the accomplishments of basic research conducted by academia etc. with practical application at Translational and Clinical Research Core Centers (Centers for Advancing Translational Research and Clinical Research Core Hospitals).

In order to support the development of drugs and medical devices, the Translational and Clinical Research Core Centers secure human resources specialized in pharmaceutical affairs, biostatistics, project management, intellectual property, as well as provide biomarker evaluation equipment, cell processing facilities, and management centers securely handling clinical study data, supporting processes from the basic research stage through clinical studies, clinical trials, and practical application of research seeds generated by Translational and Clinical Research Core

Centers and other research institutions. Furthermore, the Translational and Clinical Research Core Centers run programs to foster the young human resources taking on R&D into drugs and medical devices and medical entrepreneurs, and host seminars and symposia for those aiming to achieve practical application in medical fields.

The various services, consultations and shared facilities provided by the Translational and Clinical Research Core Centers are not restricted to within its centers and hospitals, but can also be used by a wide range of researchers ranging from those of external research institutions to corporate researchers including those of ventures. (There are charges for part of the support business and services according to the regulations of each organization.) For programs in which disbursement of Academic Research Organization (ARO) support expenses as research expenses is approved, those wishing the support of Translational and Clinical Research Core Centers when planning and implementing research aimed at the practical application of medical seeds are requested to refer to the contact points provided in the List of Translational and Clinical Research Core Centers* provided below.

* List of Translational and Clinical Research Core Centers
https://www.amed.go.jp/program/list/16/01/001_ichiran.html (in Japanese)

13.9 Registration of Researcher Information on researchmap

researchmap* is one of the largest database of researchers in Japan. It enables researchers to publicize their registered accomplishments. 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 to repeatedly input information in multiple application forms about accomplishments and applications on various databases, also leading to greater efficiency.

It should be noted that 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 on their own initiative.

* https://researchmap.jp/?lang=en

13.10 Deposit of Developed Resources in Domestic Resource Centers

It is strongly recommended that after using bioresources developed under this program and publishing the research accomplishments obtained via academic papers, etc., the persons implementing this program are to deposit[1] the relevant bioresources in domestic resource centers[2], and make them broadly available for researchers' use.

[1] "Deposit": Procedure for permitting the use (storage/provision) of resources at domestic resource centers etc. listed in 2 below 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 citation in academic papers, etc., for users receiving the relevant resources.

[2] Domestic public centers conducting deposit, storage and provision such as The National Bioresource Project (NBRP), RIKEN BioResource Research Center, National Institutes of Biomedical Innovation, Health and Nutrition, universities, etc.

13.11 Cooperation with Databases

(1) Publicizing of data from the NBDC

The Life Science Database Integration Project (https://biosciencedbc.jp/en/), having been implemented by JST's Bioscience Database Center (NBDC), is promoting the integrated use of life science databases created by an array of research institutions. “The State of Progress and Future Direction of the Life Science Database Integration Project” that was published on January 17, 2013, states that an expansion of the programs eligible to receive data and databases will be implemented with the NBDC (currently the Department of NBDC Program) playing a central role.

Based on the above, we request your cooperation in providing and releasing the following types of data and databases related to the life science field obtained through this project.

No.	Type of data	Publication platform	Publication platform URL
1	Outline of the database created for publication	Integbio Database Catalog	https://integbio.jp/dbcatalog/?lang=en
2	Data recorded in the database created for publication	Life Science Database Archive	https://dbarchive.biosciencedbc.jp/index-e.html
3	Data or databases concerning humans from 2above	NBDC Human Database	https://humandbs.biosciencedbc.jp/en/

(2) Registering with the Patient Registry Database Search System

By using a disease registry system (patient registry) in clinical development the Clinical Innovation Network (CIN) aims to vitalize clinical development of drugs and medical devices in Japan, and is a project led by the Ministry of Health, Labor and Welfare in which the environmental preparations are made by an industry-government-academia alliance. Through the promotion of the use of a disease registry system (patient registry) the National Center for Global Health and Medicine creates an information search system regarding the patient registries in existence in Japan as a part of support for efficient clinical development of drugs and medical devices, and makes this available to the general public (https://cinc.ncgm.go.jp/) (in Japanese). Those working on R&D projects related to patient registries and cohort studies (not including clinical trials and intervention studies) who have yet to register with the system are requested to do so.

(3) Other

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

13.12 Reform of Competitive Research Founding

In response to the 6th Science, Technology and Innovation Basic Plan, and the Integrated Innovation Strategy 2022 and the Comprehensive Package for Research Competitiveness Enhancement and Young Researcher Support, the government is currently discussing improvements to the system regarding competitive research funding in order to enable greater efficiency and effectiveness in the utilization of competitive research funding. In the event that, during the term of the Calls for Proposals, guidelines etc. common to other competitive research funding programs

concerning improvements to such programs and their management are presented, notice will be provided again if they are applied to the solicitation and management of this program.

13.13 Improvement of Incentives for Doctoral Students

Under the 6th Science, Technology, and Innovation Basic Plan (Cabinet decision of March 26, 2021), aiming to increase three-fold the number of doctoral students receiving the amount equivalent to living expenses (equivalent to about 30% of all doctoral students receiving the amount equivalent to living expenses) was cited as a numerical target in order to attract excellent students and working adults from Japan and overseas, and enhance the financial support of graduate students and in particular doctoral students. In addition, the Basic Plan states that in order to promote the payment of salaries to doctoral students at an appropriate level for research assistants (RA) from competitive research funds and joint research funds, the government will formulate rules for the payment of RA expenses relating to employment and remuneration for RAs at each business and university, and implement them sequentially from FY2021, and urges the expansion of the employment of doctoral students as RA at universities and research and development agencies, and the improved treatment of doctoral students.

In addition, the Guidelines on Employment and Fostering of Postdoctoral Students (formulated on December 3, 2020, by MEXT's Council for Science and Technology's Committee on Human Resources) state as follows with regard to doctoral students:

> While being students, doctoral students also have the facet of being researchers, and improving the environment for research activities and employment status is an important responsibility of universities as the fosters of researchers. (…) It is particularly vital that the contributions of doctoral students are appropriately evaluated by setting wages appropriate to the nature and content of work and the payment of salaries corresponding to the amount of time they have spent on work. (…) It is essential that universities, etc. budget as direct costs the requisite expenses in the event that they employ RAs when applying for competitive research funds, and that they conduct reviews and so on of their internal regulations in order to enable the payment to RAs of an acceptable level of wages.

In the light of that fact, in this program the doctoral students requisite for the execution of the research should be enthusiastically employed as RAs, etc. At the same time, unit costs fitting to the nature and content of their work should be set, and it is requested that doctoral students be paid a salary in accordance with the time they spend working under appropriate work management. It is also requested that when applying for this program applications are made with a funding plan paying due consideration to the salary levels of the above-mentioned doctoral students.

Points to Note

- Under the 6th Science, Technology, and Innovation Basic Plan the amount equivalent to living expenses of doctoral students is set as a minimum of 1.8 million yen per year. Furthermore, in order that excellent doctoral students can apply themselves to their research without feeling any financial concerns, the Basic Plan states the wide-sweeping expansion of those receiving around 2.4 million yen per year, equivalent to the stipend paid through the JSPS Research Fellowship for Young Researchers (Doctoral Course Students (DC)) program.
- With regard to the employment of doctoral students in order to execute research projects, the Guidelines on Employment and Fostering of Postdoctoral Students state that "Considering the average salary of assistant professors

without tenure who are employed in competitive research funds etc., it is thought that the payment of an hourly wage of around 2,000 yen to 2,500 yen would be a standard amount."

* Considering the average salary of assistant professors without tenure who are employed in competitive research funds etc., it is thought that the payment of an hourly wage of around 2,000 yen to 2,500 yen would be a standard amount. (The August 2020 bulletin edition of the Survey on The Employment Status of Instructional Staff Members at Research Universities calculates the hourly wage of doctoral students by dividing the median value of the monthly salaries of assistant professors without tenure (between 400,000 and 450,000 yen) by a 19- to 20-day shift (excluding holidays etc.) of seven and three-quarter hours to eight hours, and subtracting 20% in consideration of the recipients' status as doctoral students.)

- Research institutions are requested to decide by themselves the specific amounts and period the doctoral students will be paid. Salary payments of either a higher or lower amount than the salary level indicated above are permissible.
- When employing a doctoral student as an RA pay consideration to ensuring they do not work excessive hours and allow the doctoral students to maintain a balance with their own research and studies.

13.14 Securing of an Autonomous and Stable Research Environment for Young Researchers

The Guidelines on Employment and Fostering of Postdoctoral Students (formulated on December 3, 2020, by MEXT's Council for Science and Technology's Committee on Human Resources) state that: "The appointments for many postdoctoral students are for less than three years, and since terms of appointment that are too short may hinder their career development, it is necessary to secure tenures of a certain length in which postdoctoral students can concentrate on their research activities in a settled manner." The guidelines also state that: "In consideration of the fact that it is desirable for researchers, after having gained postdoctoral experience in one or two locations, to proceed to the next stage in the three to seven years before they reach their mid-30s, ideally terms of appointment lasting between three to five years should be secured for each post."

In addition, with regard to national university corporations and inter-university research institute corporations, the "Guidelines on Personnel Salary Management Reform at National University Corporations etc.: Towards the Creation of Personnel Salary Management that are Attractive and Contribute to Improving Education and Research Capabilities" (formulated on February 25, 2019 by MEXT) state that "In order to achieve the twin perspectives of fostering young researchers and stable employment, even in the cases of fixed tenures, by using expenses with a high degree of freedom such as indirect costs and donations, it is to be hoped that certain terms of employment of between five to ten year are secured, and systems that maintain flexibility while incorporating researcher-fostering perspectives are designed and promoted."

In the light of all of the above, in the event that young researchers such as specially appointed faculty members and postdoctoral fellows are employed in this program please strive to secure tenures of the length equivalent to the duration of the R&D, having checked with the persons in charge of personnel and accounts in the relevant department. Also, to the greatest extent possible, please endeavor to secure appointments of a certain term (about five years or more) by preventing short-term appointments through utilizing other external funding such as indirect expenses, basic expenses and donations.

13.15 Research Activities Conducted at Their Own Initiative by Young Researchers Engaged

In line with the Implementation Guidelines Concerning Research Activities Conducted at Their Own Initiative by Young Researchers Employed for Project Implementation Using Competitive Research Funds (revised on December 18, 2020 at the Liaison Meeting of Relevant Ministries on Competitive Research Fund), and with regard to the certain degree (set at a ceiling of 20%) of effort made by young researchers who are engaged in this program and whose personnel costs are paid by this program, in the event that the PI etc. judge that the young researcher's own initiative does not obstruct the R&D in question but at the same time contributes to it, the consent of their institution of affiliation is obtained it is possible to allot that effort to activities that contribute to research activities conducted at their own initiative or improvements in research and management capabilities. For more details please refer to the Administration Manuals and Forms* in the Program Administrative Procedures (Forms and other documents) section of the AMED website.

* https://www.amed.go.jp/keiri/index.html (in Japanese)

13.16 Support for Diverse Career Paths for Young Researchers

The 6th Science, Technology, and Innovation Basic Plan (Cabinet decision of March 26, 2021) cites as one of its objectives the creation of "an environment where talented young people can expect to be active in various fields such as academia, industry, and administration." In addition, the Guidelines on Employment and Fostering of Postdoctoral Students (formulated on December 3, 2020, by MEXT's Council for Science and Technology's Committee on Human Resources) state: "It is essential that doctoral human resources with sophisticated professionalism and excellent research capabilities are active in a variety of places including venture businesses and global corporations, and that they create innovation. Initiatives towards the diversification of career paths after the completion of post-doctoral terms are imperative." In response to this statement, those involved in the projects adopted by this program are requested to pursue positive initiatives to secure a variety of potential career paths for young researchers such as specially appointed professors and postdoctoral fellows employed using the competitive research 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.

13.17 Securement of University Research Administrators (URAs) and Other Management Personnel

The 6th Science, Technology and Innovation Basic Plan (Cabinet decision of March 26, 2021) pointed out the importance of initiatives regarding assuring quality as a professional occupation and improving treatment in order to make URAs and other management personnel an attractive profession. Furthermore, the Comprehensive Package for Research Competitiveness Enhancement and Young Researcher Support (formulated by Council for Science, Technology and Innovation on January 23, 2020) indicates the necessity of establishing career paths for management personnel, URAs and engineers etc.

Based on the above, in the event that URAs and other management personnel employed at or newly employed by research institutions are dedicated to working on the management of this program's research projects, research institutions are requested, to the greatest extent possible, to endeavor to secure appointments of a certain term in order to prevent short-term appointments for such personnel through funding not exclusively from this program but also from indirect costs of external funds, basic expenses and donations and so on.

In conjunction with this, as a form of support towards securing career paths for the management personnel in question, it is requested that enthusiastic initiative are pursued such as gaining participation in URA training etc. Please also consider the utilization of indirect costs for these initiatives.

13.18 Accreditation of Partnership on Research Assistance Service (A-PRAS)

This is an announcement about research support services. The “Development of Science and Technology Innovation Policy Towards the Creation of Knowledge-intensive Value: Towards a Nation that Leads the World in Achieving Society 5.0 (final summary)” (formulated on March 26, 2020, by MEXT’s Council for Science and Technology’s Comprehensive Policy Special Committee) states that “There is a need for the creation of new public private partnership (PPP) mechanisms based on the emergence of start-ups conducting their business with a strong determination and passion for returning to society the accomplishments of research assistance and research results from projects implemented as public projects by the government.”

In the midst of these circumstances, MEXT established the Accreditation of Partnership on Research Assistance Service (A-PRAS) in FY2019 with the objectives of improving the research environment, accelerating the promotion of science and technology and the creation of innovation in Japan, and supporting the development of various schemes regarding research assistance services. This system provides the accreditation by the Minister of Education, Culture, Sports, Science and Technology of services - among the research assistance services conducted by private sector businesses - that satisfy certain conditions. As of the end of FY2020 nine services had been accredited.

Details of the accredited services can be viewed at the MEXT webpage* shown below. It is very much hoped that this service will be widely used.

* https://www.mext.go.jp/a_menu/kagaku/kihon/1422215_00001.htm (in Japanese)

Chapter 14. Contact

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 Innovative Research and Development, Department of Innovation and Clinical Research Center, AMED Tel: +81-3-6870-2224 E-mail: kenkyuk-kobo "AT"amed.go.jp
Misconduct/fraudulent use/fraudulent receipt	Division of Research Integrity, Social Co-Creation and Legal Affairs, Department of Research Integrity and Project Management, AMED E-mail: kouseisoudan "AT"amed.go.jp
Management of conflict of interest/responsible conduct of research (RCR) education programs	Division of Research Integrity, Social Co-Creation and Legal Affairs, Department of Research Integrity and Project Management, AMED E-mail: kenkyuukousei"AT"amed.go.jp
RIO Network	Division of Research Integrity, Social Co-Creation and Legal Affairs, Department of Research Integrity and Project Management, AMED E-mail: rionetwork"AT"amed.go.jp
Medical IP Desk (Contact point for medical IP consultation)	Division of Intellectual Property, Department of Intellectual Property and Technology Transfer, AMED E-mail: medicalip"AT"amed.go.jp
Support provided by the AMED Drug Discovery Support Network/Department of Innovative Drug Discovery and Development	East Japan Office, Department of Innovative Drug Discovery and Development, 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: 0570-057-060 (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 (NBDC) Tel: 03-5214-8491 E-mail: nbdc-kikaku"AT"jst.go.jp

Chapter 15. (Reference) Research and Development Objectives

15.1 Elucidation of stress responses and pathogenic mechanisms

1. Objective Title

Elucidation of stress responses and pathogenic mechanisms

2. Overview

Preventing the onset of diseases caused by the various emotional, physical, or chemical stressors that exist in our society and environment is an important part of improving quality of life (QOL) for the entire nation. However, it is difficult to grasp in detail how the body responds to various types of stress and there are still numerous unknowns with exposure to stress and pathogenic mechanisms. We are therefore not yet in a position to prevent disease through early detection of the body's alarm signals in response to stress exposure. For these reasons, this strategic objective is aimed at developing a scientific and comprehensive understanding of the phenomena that occur in response to stress at both a cellular and an individual level and elucidating the pathogenic mechanisms involved, through joint research involving close collaboration between researchers in basic life science research fields and in clinical medicine.

3. Aims

We need to research the relationship between the various types of emotional, physical, or chemical stressors that exist in our society and environment if we are to prevent disease or facilitate early interventions. However, at present it is difficult to form an objective understanding of the impact on the body from the various types of stress in our surroundings and there are still numerous uncertainties over what degree of stress exposure results in homeostatic breakdown in the body and leads to pathogenesis in which many unknown mechanisms involved. We are therefore not yet in a position to detect at an early stage the body's alarm signals when exposed to stress and take the necessary steps to prevent disease.

On the other hand, with regard to methods for understanding the body's perception of risk to stress exposure, recent advances in sophisticated measurement instruments and wearable devices have made it much easier than before to measure biological responses accurately and over long periods of time. Thus, the foundation has been laid for further research in this area.

The Second Phase of Japan's Healthcare and Medical Strategy (decided by the Cabinet Office on 27 March 2020, partially amended on 9 April 2021) highlighted the importance of building health and medical systems that focus on disease prevention, disease management, and living with diseases. The Sixth Basic Plan for Science, Technology and Innovation also described the need for programs to prolong active social participation; this means as well as promoting longer healthy life expectancy, Japan needs to help people actively engage in society at any age so that more people are healthy in their 100s and lead full lives. This shows how longer healthy life expectancy and progress in preventive medicine are positioned as important goals in government policy.

Research into these issues is already underway in various fields in Japan, as shown by the inclusion of sessions on stress at various academic conferences, such as meetings of the Japan Endocrine Society or the Japanese Society of Neurology. However, looking at trends in the global literature on stress, we can see that although Japan is producing

a lot of research at the cellular level, the country tends to be less competitive when it comes to research at the individual level.

Research at the cellular level that observes cell responses to emotional, physical, or chemical stressors is an important element-reduction approach to understanding stress response mechanisms in the cell. However, experimental observations of cells under stress in the test tube do not tell us much about the various symptoms or diseases in the organs when the individual is exposed to stress. When the stress responses observed at the cellular level actually occur in vivo, we need to be able to evaluate what phenomena these responses cause at the individual level.

In contrast, with research at the individual level such as cohort research, we can uncover stress factors that are closely correlated to organ symptoms or disease. However, it can be difficult to understand how the emotional, physical, or chemical stressors that the individual is exposed to are converted into stress at the cellular level within the body, and how stimulation of the various cells triggers a cell stress response; we do not know how the stress at the individual level is reflected within the body in cellular-level phenomena. For this reason, with research only conducted at the individual level, it is difficult to identify candidate targets for drug discovery based on molecular mechanisms or to establish stress markers that play a role in stress avoidance or disease prevention based on scientific or biological evidence. We need to understand how stress exposure at the individual level is interpreted as stress information at the molecular and cellular level, and we need to elucidate the cell response mechanisms and connect this to an understanding of the factors involved in organ symptoms.

As such, in order to understand the mechanisms of disease onset caused by stress, it is not enough to pursue only cellular-level research or individual-level research; we need to conduct research that integrates phenomena at the cellular level with phenomena at the individual level.

To be able to elucidate the pathological mechanisms in humans caused by emotional, physical, or chemical stress in our society and environment and to apply this to preventive medicine, we need to progress our understanding of the relationship between stress and disease, and we need joint research conducted through close collaboration between basic researchers and clinical researchers to combine research investigations at the cellular level with those at the individual level.

When pursuing research to help everyone remain in good health, it is important to have a scientific understanding of the relationship between stress and disease, including an understanding of the connections between the cellular level and the individual level. This should be a key research area today.

4. Goals and Objectives

Under this Research and Development Objective, the goals are to develop an integrated understanding of phenomena from the cellular to the individual level and a scientific assessment of stress responses at each level (from cellular to individual) caused by various types of stress, including emotional stress. Further goals are to develop measuring technologies capable of capturing subtle biological information in an accurate and detailed manner over long periods of time and to identify new stress markers for objective indicators of stress exposure. Specifically, this Objective aims to achieve the following:

(1) Elucidation of the mechanisms involved when the body comes under stress and systems for stress adaptation

or avoidance break down and disease occurs, with a view to applications in prevention of disease onset

(2) Identification of predictive markers of disease due to stress exposure and elucidation of the biological significance and mechanism of action of these markers at a molecular and cellular level as a stress response

(3) Development of new measuring devices capable of detailed, long-term measurements of the subtle fluctuations in biological information in response to stress in humans

5. Future Vision for Society That Should Be Taken into Account

By achieving the Objectives set out in section 4, it should be possible to objectively detect at an early stage the impacts of stress exposure, and this should help us to either prevent diseases caused by stress or discover and treat them in the early stages. This should allow everyone to lead a healthy and safe life where they can participate in society.

6. For Reference

6-1 Domestic and International Research Trends

A review of global trends in the literature on stress research shows that Japan ranks fourth in the world in terms of the number of papers published on cellular-level research, but we become less competitive for research at the individual level (ranking 11th in the world for the number of papers published; the US leads the way in this field and ranks first for both cellular-level and individual-level research).

Domestic Trends

While stress has previously been researched as part of the AMED-CREST program “Innovation for Ideal Medical Treatment Based on the Understanding of Maintenance, Change and Breakdown Mechanisms of Homeostasis among Interacting Organ Systems” (2012–2019) and the MEXT Scientific Research on Innovative Areas “Living in Space: Integral Understanding of Life-Regulation Mechanisms from SPACE" (2015–2019), to date there has not been a major basic research project focused on stress. A wide range of research is underway, as shown by the inclusion of sessions on stress at various academic conferences, such as meetings of the Japan Endocrine Society or the Japanese Society of Neurology, plus the presentation of research results and information exchange.

In Japan, research into oxidative stress in cells has generated substantial results, but research at the individual level has involved questionnaire-based research in humans or cohort research and the results generated are not yet understood in terms of the underpinning molecular or cellular phenomena. This has been a significant bottleneck in the promotion of research in this area.

International Trends

The National Center for Complementary and Integrative Health (NCCIH) in the US provides support for research into various types of stress, one example being the study “Exposure to stressors and the development of resilience in National Guard recruits during Basic Combat Training and their first 2 years of service.” The National Institute of Mental Health (NIMH) is also promoting stress research, such as the Traumatic Stress Research Program.

Over the past few years, the concept of the “exposome” has come under the spotlight overseas. The exposome is an indicator that describes all the environmental exposures that an individual encounters throughout life and how that

may influence human health. There is growing interest in this concept, as demonstrated by the inclusion of exposome research on the website of the Centers for Disease Control and Prevention (CDC) in the US or the establishment of the European Human Exposome Network in Europe. Scientists in the West are working to understanding stress in terms of the exposome and marry this with biological phenomenon. Stress research is therefore drawing attention worldwide.

6-2 History of the investigations

The following investigations have been conducted, based on the Guidelines for the Establishment of Strategic Objectives (decided at the July 2019 Meeting of the Basic Research Promotion Division, Research Promotion Bureau, MEXT).

1. A questionnaire on what potential research trends was developed based on materials from a database of analysis and research papers on research trends in Japan, which used the Kaken Grants-in-Aid for Scientific Research Database and other sources. The questionnaire was sent to specialists participating in the expert network of the Science and Technology Foresight Center at the National Institute of Science and Technology Policy (NISTEP), the various units of the Center for Research and Development Strategy (CRDS) at the Japan Science and Technology Agency (JST), and Program Directors at the Japan Agency for Medical Research and Development (AMED).
2. The completed questionnaires were analyzed with reference to information presented at academic conferences in life sciences and medicine. The results showed recognition of the importance of research to understand the body's response to stress and elucidate the relationship between stress and disease onset. The Objective "Elucidation of mechanisms for stress responses to disease development" was therefore identified as a research trend that should be focused on.
3. In November 2022, MEXT and AMED co-hosted a workshop that brought together industry and academic experts working on stress responses and pathogenic mechanisms to discuss (1) the latest notable research trends on stress in Japan and overseas, (2) how the range of stressors for this R&D Objective should be defined, (3) how scientific research to connect phenomena at the cellular level with those at the individual level should be advanced, and (4) how the results from model animal studies should be linked in with research in humans. These workshop discussions and other expert briefings were then used to inform the formulation of this Research and Development Objective.

6-3 Relevant Descriptions Included in Japanese Cabinet Documents

The Second Phase of Japan's Healthcare and Medical Strategy (decided by the Cabinet Office on 27 March 2020)

3.2 Basic Policy on Creating New Industries and Promoting International Development to Contribute to the Formation of a Society of Health and Longevity

Building health and medical systems that focus on disease prevention, disease management, and living with diseases

- The goal is to build healthcare and medical systems that focus on disease prevention, disease management, and living with diseases (systems that help improve QOL and promote individual behavior change through a collaboration between government, industry, and medical and nursing care experts to develop seamless

connections between healthcare settings and daily life settings, and keeping in mind the management of multifactorial diseases).

6th Science, Technology and Innovation Basic Plan (decided by the Cabinet Office on 26 March 2021)
Chapter 1 3. (1) (ii) A Society in which individuals can realize diverse wellbeing

- Japan needs programs to prolong social participation; this means as well as promoting longer healthy life expectancy, Japan needs to help people actively engage in society at any age so that more people are healthy in their 100s and lead full lives.

Plan for the Promotion of Medical Research and Development (decided by the Headquarters for Healthcare Policy on 27 March 2020)
1.2 Awareness of current status

- This document highlighted that for prevention, Japan needs to engage with programs not only for secondary prevention (early detection and early treatment of disease) and tertiary prevention (once a disease has occurred, receive the necessary treatment to maintain and restore function, and prevent relapse or complications), but also for primary prevention (promote good health by improving lifestyle habits, preventing lifestyle-related diseases).

7. Miscellaneous

Connecting basic research to clinical perspectives is a key element in this Research and Development Objective, and we look for collaborations with academic societies that are implementing these activities.

Researchers will need to make detailed measurements of biological information in order to pursue this Research and Development Objective, so we also look for collaborations with measurement engineering-related fields.

15.2 Elucidation of the mechanisms relating to changes in biological robustness associated with aging and control of age-related diseases

1. Objective Title

Elucidation of the mechanisms relating to changes in biological robustness associated with aging and control of age-related diseases

2. Overview

One urgent issue in Japan, which is experiencing the most rapidly aging society in the world and is entering a super-aging society, is achieving extended life expectancy by reducing the gap between the average life expectancy and healthy life expectancy and ensuring a longer healthy life expectancy in order to improve the QOL of the elderly and to suppress the increase in medical expenses.

In this objective, in order to accelerate efforts toward the realization of a longer healthy life expectancy, we will develop the research findings on the aging mechanism, etc. obtained thus far, and contribute to elucidating the mechanism relating to the control of age-related diseases, etc. In addition, by utilizing cutting-edge technologies such as advanced measurement and analysis technologies and exploring the fundamental principles of aging, we will promote new aging research based on the mechanism of the basic principle of aging itself. Through these, we will contribute to the search for new seeds, the prevention of age-related diseases, and the development of therapeutic agents.

3. Goals and Objectives

Under this strategic objective, the aim is to conduct research to understand the principles of the biological phenomenon of aging and to build a close-knit system for research collaboration that contributes to the prevention and treatment of age-related diseases. A further aim is to combine with research in other fields to pursue new approaches to aging research that utilize the most up-to-date methods. In particular, the following three targets are to be achieved:

(1) Clarification of the mechanisms involved in age-related disease onset, prevention, and treatment

(2) Integrated understanding of the aging control mechanisms involved in the body's robustness to disease

(3) Basic understanding of age-related changes in the body's robustness using the most up-to-date technologies

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

The achievement of "3. Goals and Objectives" should contribute to our society as outlined below through an understanding of the Aging biology in the sense of change in the body's robustness and advances in cutting-edge technologies, as well as the creation of new innovations that can lead to the prevention and treatment of age-related diseases.

- Society where all people can lead active lives, in good physical and mental health
- Society with even longer healthy life expectancies where people live into their 100s through evidence-based improvements in daily lifestyle habits and the prevention, diagnosis, and treatment of disease

5. Specific Research Examples

To achieve "3. Goals and Objectives", AMED will promote research to contribute to the clarification of aging control mechanisms and the prevention and treatment of age-related diseases based on these principles, while Japan Science and Technology Agency (JST) will pursue research to clarify the principles of the biological phenomenon of aging. AMED and JST will operate an integrated program to achieve this strategic objective, working in partnership on the research pursued by each organization.

(1) Clarification of the mechanisms involved in age-related disease onset, prevention, and treatment

- Clarification of the aging mechanisms involved in age-related diseases, including vascular disease and metabolic abnormalities
- Investigation into biomarkers of age-related diseases (e.g., sarcopenia and frailty) and elucidation of mechanisms to contribute to prevention and treatment

(2) Integrated understanding of the aging control mechanisms in the body's robustness to disease

- Utilizing animal models etc. to understand aging control mechanisms involved in disease, taking into consideration the involvement of molecules/cells (populations), organs, and the entire body
- Utilizing animal models etc. to identify aging molecules and substances that act on aging control factors involved in disease and to elucidate mechanisms of action

(3) Basic understanding of age-related changes in the body's robustness using the most up-to-date technologies

- Utilizing cutting-edge technologies, such as genome omics, spatial omics, imaging, data analysis, genome editing, and molecule/cell/gene manipulation technologies, to:
  - Focus on a diverse range of biological phenomena to clarify the mechanisms whereby the body's robustness is maintained or changes during aging
  - Clarify variation in aging between individuals and shared mechanisms, based on environmental and genetic factors, in model animals etc.
  - Understand the basic principles that determine aging and life spans using non-animal models with specific traits related to aging

* Because of the nature of research into aging, it can take time to prepare resources etc. to conduct the research, so it is expected that the research will be conducted along with the required support and in collaboration with other projects etc. in order to promote the participation of young researchers and researchers from other fields

6. Domestic and International Research Trends

Aging research already underway includes basic research to understand the aging phenomenon using molecular biology and other approaches, as well as research looking at the control of age-related diseases including into control mechanisms and disease prevention, diagnosis, and treatment. As a result, we are gradually developing a deeper understanding of how to control age-related diseases by removing senescent cells or mechanisms to control aging involving the CNS network or relevant organs.

There has been marked progress in recent years in biological measurement and analytical technologies and these research methods could allow dramatic advances in our understanding of the mechanisms of aging.

In the future, integrated research organizations may be developed to pursue comprehensive research aimed at both basic research and applied research on prevention and treatment, in order to explore the fundamental principles of aging using these advanced technologies and clarify the mechanisms for prevention and treatment of age-related diseases in light of these principles.

Domestic trends

Under the Project for Elucidating and Controlling Mechanisms of Aging and Longevity (AMED) and JSPS Grants-in-Aid for Scientific Research, research is already underway on metabolic network control and the relationship between biological clocks and life span mechanisms, using model animals, and into organs during aging and brain-organ networks. Combined with recent advances in measurement and analytical technologies (e.g., omics) and in big data and AI analytical technologies , substantial progress has been made in our understanding of aging phenomena at the molecular, cellular, and whole-body levels.

International trends

Aging research has become an active field internationally. For example, in 2021, the National Institutes of Health (NIH) in the US established grants for a new project called Cellular Senescence Network (SenNet) to pursue aging research. A number of studies are underway, also in the US, including a clinical study using NMN that activates sirtuin enzymes, which are thought to delay aging and prolong healthy life years, and the Targeting Aging with Metformin (TAME) trial that is investigating whether the widely used diabetes drug metformin can also be used to delay the onset of age-related diseases like cancer, cardiovascular disease, and neurodegenerative disease and whether it can prolong healthy life years.

7. History of the Investigation

Investigations were conducted as described below, based on the Policy on Defining Strategy Targets (decision dated June 2019 by the Council for Science and Technology, Basic Research Promotion 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, highlighted the significance of a basic understanding of changes in the body's robustness; an understanding of aging control mechanisms and the mechanisms involved in the onset, prevention, and treatment of age-related diseases; and the growing need for basic research to accelerate aging research. "Understanding changes and recovery mechanisms in the body's robustness during aging and exploration of control methods" was

therefore specified as a key research trend.

3. In October 2021, the Ministry of Education, Culture, Sports, Science and Technology (MEXT), JST, and AMED co-hosted a workshop that brought together experts from the relevant industries and academia involved in understanding changes and recovery mechanisms in the body's robustness during aging and exploration of control methods. Discussions covered key R&D strategies in Japan, the possible social and economic impact, and strategies to maximize research outcomes. These workshop discussions were used to develop the strategic objectives and R&D objectives.

8. Relevant Descriptions Included in Japanese Cabinet Documents

The Healthcare Policy (Cabinet decision dated April 2021 (partially revised))

3. Basic Policy

Focus on development objectives (prevention/diagnosis/treatment/convalescence, QOL) and select best approach for the target of extending healthy life years to build a healthy long-lived society

4. Specific Measures

- Conduct basic research and development for a functional understanding of brain function, immunity, and biological phenomena like aging and to elucidate disease mechanisms targeting various different diseases, with the aim of applying these findings to research and development in medical fields.
- Lay the foundations to support an integrated cycle of research, from basic to applied research, by taking the above research and development outcomes and linking them to R&D in clinical research programs or other comprehensive projects and also conducting research and development that involves clinical themes.

9. Miscellaneous

A number of programs of relevance to this Objective are already in existence, including AMED's Project for Elucidating and Controlling Mechanisms of Aging and Longevity (FY2017–21) and JST's Strategic Objective "Creation of integrated single cell analysis fundamental technology to contribute to the elucidation of biological functions" (FY2014–21), and we expect the outcomes from these programs to be utilized and progressed as well.

The plan is to progress this Objective through proactive interaction with the Moonshot Research & Development Program's Goal No. 7 "Realization of sustainable care systems to overcome major diseases by 2040, for enjoying one's life with relief and release from health concerns until 100 years old" (FY2020–29) and with the AMED R&D Objective "Clarification of the mechanism of individual's functional impairment over the entire life course" (FY2017–24).

For this project, JST and AMED will simultaneously initiate a research area and R&D area under this common Objective and will work together to pursue new research into aging. Specifically, we hope to achieve the following through further inter-organizational collaboration. We hope to see the use of the expertise gleaned from the collaborative system involving JST and AMED under the FY2021 strategic objective and R&D objective of "Integrated understanding of human multi-sensing networks and elucidation of their control mechanisms" an example of which would be allowing duplicate applications. We also hope that new joint research by both organizations'

researchers will be initiated, that young researchers will emerge and flourish, and that these factors will lead to the ultimate goal of boosting collaboration in both basic research into aging and research aimed at application in disease prevention and treatment.

15.3 Immunological memory: Understanding, regulation and medical innovation

1. Objective Title

Immunological memory: Understanding, regulation and medical innovation

2. Overview

The SARS-CoV-2 pandemic has reaffirmed the importance of human immunization research, but basic research on immunology to date has mostly been performed using mice and has focused on investigating short-term immune responses. Although the analysis of cell and molecular mechanisms relating to the immunological memory phenomenon, which is the basic principle of vaccines, is progressing using a mouse model, there are still many unclear points about the human immunological memory. Immunological memory is an important host defense system that functions against infectious microorganisms, but is also closely implicated in the pathogenesis of various diseases, including cancer and allergy/autoimmune disease. Immunological memory is a potential target for the development of clinical methods to predict, prevent, and treat such diseases, so a better understanding of the mechanisms will be vital to lay the foundations for medical advances in the management of these diseases. Creation of new concepts of immunological memory will be expected by investigating the mechanism on the establishment of memory based on recognition of self and non-self, memory against pathogenic and symbiotic microorganisms, and pathogenic memory vs. beneficial memory.

The goal of this R&D objective is to create medical innovations that will contribute to predicting and regulating diseases like cancer, infectious disease, and allergy/autoimmune disease, through a hierarchical and multifaceted understanding of immunological memory in humans by applying advanced research technologies such as the recently developed single-cell/repertoire analyses and structural analyses using cryo-electron microscopy, bioinformatics, AI, epigenetics, etc.

3. Goals and Objectives

This R&D objective aims to integratively understand the immunological memory that are closely involved in cancer, infectious disease, and allergy/autoimmune disease, etc. by using the latest, most-advanced research technologies, and to create medical innovations to predict and control these diseases. In particular, the following four targets are to be achieved:

(1) A new and fundamental understanding of how human immunological memory is formed, maintained, and lost
(2) Clarification of novel mechanisms of cancer immunity mediated by human immunological memory
(3) An understanding of human immunological memory against infectious diseases in societies living with COVID-19 and after the COVID-19 pandemic
(4) Development of novel methods controlling allergic and autoimmune diseases, based on an understanding of human immunological memory

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

By achieving the Goals and Objectives described in section 3 above, we will be able to take the medical innovations thus created and apply them as new healthcare technologies to contribute to society in the following ways:

- Society with access to personalized preventive and therapeutic care for diseases where the immune system is

involved, such as cancer, infectious diseases, allergic diseases, and autoimmune diseases, through the understanding and quantification of immunological memory status.

- Society where people can live longer healthy lives after complete recovery, without relapse, from allergic and autoimmune diseases, cancer, and infectious diseases.
- Society where the rapid development of safe and effective vaccines is possible due to the accumulated knowledge relating to immunological memory.

5. Specific Research Examples

(1) Fundamental understanding of how human immunological memory is formed, maintained, and lost

- Comprehensive understanding of the mechanisms underlying the establishment of memory in lymphocytes and innate immune cells, and the regulatory mechanisms of immunological memory by Treg cells, tissue-resident immune cells, and even non-immune cells
- Development of animal models or analytical technologies that contribute to our understanding of human immunological memory
- Changes in immunological memory over the course of life and clarification of their regulatory mechanisms
- Understanding of the impact of environmental factors including microbiota on immunological memory
- Clarification of the mechanisms how memory is established and regulated in the mucosal immune system

(2) Clarification of new mechanisms of cancer immunity mediated by human immunological memory

- Clarification of novel mechanisms of cancer immunity from the perspective of immunological memory
- Clarification of mechanisms how genetically engineered immune cells control immunological memory by in ex-vivo gene therapy

(3) Infectious diseases and human immunological memory in societies living with COVID-19 or after the COVID-19 pandemic

- Understanding of immunological memory against various pathogens
- Clarification of mechanisms for immune activation and immune escape based on an understanding of immunological memory in emerging and re-emerging infectious diseases
- Development of innovations for new diagnostic, preventive, and therapeutic methods by the latest wet and dry research approaches, based on immunological memory with a particular focus on personalized medicine for infectious diseases

(4) Development of novel therapeutics for allergic and autoimmune diseases, based on an understanding of human immunological memory

- Identification of pathogenic memory cells in allergic and autoimmune diseases, and clarification of functional role of those cells in the pathogenesis of these diseases
- Development of innovations for new therapeutic methods for allergic and autoimmune diseases through the elimination of immunological memory

6. Domestic and International Research Trends

Domestic trends

AMED has initiated oncology programs including the Project for Cancer Research and Therapeutic Evolution (P-CREATE) (FY2016–21); infectious disease programs including the Program to Develop Countermeasure Technologies against Viral and Other Infectious Diseases (from FY2020) and the Advanced Research & Development Program for Medical Innovation's R&D Area "Generating Research Infrastructure and Novel Technologies for Anti-Infective Drug and Vaccine Discovery" (from FY2021); and allergic and autoimmune disease programs including the Advanced Research & Development Programs for Medical Innovation's R&D Areas "Etiological Basics of and Techniques for Treatment of Allergic and Autoimmune Diseases" (FY2008–15) and "Creation of Basic Medical Technologies to Clarify and Control the Mechanisms Underlying Chronic Inflammation" (FY2010–17). However, there has been no support for basic research across various diseases with a focus on immunological memory. The International Immunological Memory and Vaccine Forum (IIMVF) was established in 2012 and has held five international symposia to date, promoting international joint research and information exchange.

International trends

In the US, the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), has increased the amount of support provided for immunological memory projects each year. In addition, Keystone Symposia held joint conferences in March 2021 on topics such as T-cell Memory and B Cell Renaissance: Epigenetics, Regulation and Immunotherapy. These trends show the increasing focus on this field.

7. History of the Investigation

Investigations were conducted as described below, based on the Policy on Defining Strategy Targets (decision dated June 2019 by the Council for Science and Technology, Basic Research Promotion 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. Analysis of the responses from these questionnaires, as well as information from interactions with experts, highlighted the significance of an integrated understanding of the immunological memory mechanism common to infectious diseases, cancer, and allergic and autoimmune diseases and the development of methods to predict and control these diseases. On this basis, "Understanding memory that resides in the immune cells and developing control methods that will contribute to healthcare applications" was specified as a key research trend.

3. In October 2021, the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and AMED co-hosted a workshop that brought together experts from the relevant industries and academia involved in understanding memory that resides in the immune cells and developing control methods that will contribute to healthcare applications. The workshop featured discussions on the latest research trends of interest in Japan and overseas, research topics that need to be addressed in the future, the expected impacts on society and the economy, and concrete strategies in Japan. This Research and Development Objective was then created in light of the workshop discussions and expert briefings.

8. Relevant Descriptions Included in Japanese Cabinet Documents

The 6th Science, Technology, and Innovation Basic Plan (Cabinet decision dated 26 March 2021)

Chapter 3, 2

- It is expected that elucidation of disease mechanisms, development of new diagnostic and treatment methods, R&D of drug discovery using AI, big data, etc., and personalized medicine and precision medicine tailored to individual conditions will advance.

The Healthcare Policy (Cabinet decision dated 27 March 2020)

4.1.(1) Pursuing research and development

- Conduct basic research and development to clarify biological functions including brain function, immunity, and aging and various different types of disease mechanisms with the goal of applying the findings to research and development in medical fields.
- Develop new treatment methods, including gene therapies and immunotherapies, and develop diagnostic and therapeutic agents that will contribute to personalized medicine
- Research and development to contribute to the clarification of immuno-allergic disease pathologies and their prevention, diagnosis, and treatment

9. Miscellaneous

Research to understand human immunological memory will progress effectively if performed with a correct understanding of the similarities and differences between mouse and human immune systems and pursued through an efficient interaction between mouse and human researches. We strongly recommend that research not be restricted to investigations in animal models, but should involve close collaboration with clinical researchers or use human samples from biobanks. At least, your proposal needs to include plans for proof of concept (POC) research in humans/patients, to verify the findings obtained from experiments in mouse and other animal models. The goal is to create new concepts in immunological memory, and to use these concepts as the basis for innovation to develop futuristic preventive and therapeutic methods. We expect to see the research teams that mainly comprise young and mid-career researchers from not only immunology but also various research fields.

Immunological memory is a common theme in the prevention and treatment of diseases with significant immune system involvement, such as cancer, infectious disease, and allergic and autoimmune disease. As further our understanding of how immunological memory is involved in these diseases through this Research and Development Objective, we expect to see new medical innovations. In Japan, we encourage the participation of new researchers

and the dissemination of research results through collaboration with the Japanese Society for Immunology (JSI) and other relevant academic societies. We will plan to promote immunological memory research in Japan to be world-wide through the use of international platforms that allow interactions with overseas researchers (e.g., the United States-Japan Cooperative Medical Sciences Program and the International Immunological Memory and Vaccine Forum (IIMVF)).

When working towards this Research and Development Objective, we will collaborate actively with AMED's Strategic Center of Biomedical Advanced Vaccine Research and Development for Preparedness and Response (SCARDA).

15.4 Integrated understanding of human multi-sensing networks and elucidation of their control mechanisms

1. Objective Title

Integrated understanding of human multi-sensing networks and elucidation of their control mechanisms

2. Overview

The sensory organs (eyes, ears, nose, mouth), skin all over the body, deep internal organs within the torso (organs including the stomach, intestines, and liver), and the peripheral nerves that are widely distributed throughout these areas all work together to maintain functions across the body. Reduced or lost sensory faculties or peripheral neuropathy, triggered by aging, stress, or other environmental factors, are risk factors for the onset of chronic disease or health problems. An integrated understanding of multi-sensory physiological mechanisms, which include these sensory systems and peripheral nerve networks, could lead to the development of new treatment methods targeting various diseases or organs across the body, resulting in improved quality of life (QOL) and longer healthy life expectancies.

This Research and Development Objective aims to clarify the mechanisms of action in multi-sensory systems, including sensory systems and peripheral nerve networks; clarify disease pathology; and develop technologies to visualize and quantify activity status. The Research and Development Objective then aims to use these technologies to develop therapeutic and preventive methods that produce few side effects, and to create pharmaceuticals, medical equipment, and minimally invasive devices tailored to individuals. A further goal is to create seeds for innovation by expanding the body's multi-sensory functions and applying advanced sensing mechanisms.

3. Goals and Objectives

This Objective aims to develop an integrated understanding of multi-sensory systems, including sensory systems and peripheral nerve networks, and to develop methods to visualize and control these systems. Specifically, this Objective aims to achieve the following:

(1) Understand peripheral neural circuit mechanisms and clarify disease pathology to help overcome disease
(2) Develop methods to visualize and control peripheral nerve activity and new treatment methods
(3) Clarify and apply the mechanisms involved when sensory systems receive, process, and act on signals
(4) Develop technology platforms for methods to visualize and control sensory systems

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

By realizing the Goals and Objectives in section 3. above, the research will contribute to the widespread rollout across society of innovative technologies mediated by multi-sensory systems, thereby helping to achieve the following:

- A society of health and longevity due to the development of treatment methods that produce few side effects, preventive methods, minimally invasive devices, and medical equipment that involve control of the sensory system and/or peripheral nerve networks.
- Over the long term, a society capable of "sensory substitution" or "sensory sharing" developed through an integrated understanding of the senses.

5. Specific Research Examples

(1) Understand peripheral neural circuit mechanisms and clarify disease pathology to help overcome disease

- Clarification of the homeostatic mechanisms and disease pathologies of peripheral nerve networks
- Clarification of functional control mechanisms in various organs based on stimulatory regulation of the peripheral nerves
- Clarification of the mechanism of peripheral neuropathy

(2) Develop methods to visualize and control peripheral nerve activity and new treatment methods

- Detection and visualization of activity status in peripheral nerve networks, and development of new sensor devices to quantify this
- Development of methods to control peripheral nerve activity and medical applications to help overcome disease

(3) Clarify and apply the mechanisms involved when sensory systems receive, process, and act on signals

- Use of imaging technologies etc. to clarify and apply the mechanisms involved when information is received and processed between the sensory organs=>peripheral nerves =>central nervous system
- Clarification and application of the mechanisms behind sensory system actions at the cell and gene level for smell, taste, touch, and other senses
- Clarification of the sensory system mechanisms with potential for application in devices like artificial sensory organs, and clarification of the sensory system mechanisms that affect applied cognition and behavior

(4) Develop technology platforms for methods to visualize and control sensory systems

- Development of platform technologies for wide-scope, real-time visualization and quantification of the activity state of sensory systems
- Development of platform technologies for sensory system control and utilization

6. Domestic and International Research Trends

Recent research has shown that damage to sensory systems and peripheral nerve networks not only reduces QOL, but also has a direct and indirect involvement in the onset and progression of lifestyle diseases, dementia, or cancer. Future technological advances, for example in optogenetics, genome editing, sensory organoids, or high-sensitivity Ca2+ imaging, are expected to allow dramatic progress in our understanding of the mechanisms involved when sensory systems receive, process, and act on signals or the mechanisms in interorgan networks mediated by peripheral nerves. This should also lead to the rapid development of applications in medicine.

Domestic trends

Research thus far into sensory systems and peripheral nerve networks has mostly involved standalone projects conducted by individual researchers. In the past few years, more research results have been generated through the application of innovative world-class Japanese technologies, such as imaging, genetic engineering, regenerative medicine, omics analysis, materials technologies, ultrafine processing, and robotics. The establishment of a large-

scale R&D area that includes all these standalone research projects is expected to promote collaboration between and the merging of individual research projects, a better understanding of mechanisms of action and disease pathology, and the development of innovative and minimally invasive medical equipment/devices and healthcare systems.

International trends

Overseas, in 2014, the US National Institutes of Health (NIH) and GlaxoSmithKline (GSK) established the field of electroceuticals, which combines the studies of medicine, biology, and engineering, and have engaged in research aimed at understanding physiological mechanisms in the peripheral nerves and using this knowledge to develop new treatment methods. In 2016, GSK formed a joint venture with Google (Galvani Bioelectronics) and this company has filed multiple patent applications since then. Research institutions in Europe and the US are becoming actively engaged in research in this field. The WHO published its first World Report on Vision (2019) and is preparing a World Report on Hearing; both these reports describe the need for prevention and treatment. In 2019, Gordon Research Conferences held a Bioelectronics conference, underlining how the new research field of peripheral nerves and the development of devices that act through the peripheral nerves is a hot topic overseas.

7. History of the Investigations

Investigations were conducted as described below, based on the Policy on Defining Strategy Targets (decision dated July 2019 by the Council for Science and Technology, Basic Research Promotion 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) As a result of further analysis with reference to the above questionnaire-based survey results and expert briefings, it was recognized that it was important to gain an integrated understanding of the mechanisms involved in sensory systems and peripheral nerve networks and to develop methods to visualize and control such mechanisms. This resulted in the identification of "Comprehensive understanding of peripheral nerve networks and elucidating biocontrol mechanisms" as a research trend to be monitored.

(3) In November 2020, the Ministry of Education, Culture, Sports, Science and Technology (MEXT) in collaboration with JST and AMED held a workshop to bring together experts in this research field from industry and academia. The workshop featured discussions on the latest trends in Japan and overseas, the direction of research and technology development, and expected social and economic impacts. This Strategic Objective was created in light of the workshop discussions and expert briefings.

8. Relevant Descriptions Included in Japanese Cabinet Documents

The Healthcare Policy (Cabinet decision dated 27 March 2020)

3. Basic policy

Focus on development purpose (prevention, diagnosis, treatment, prognosis/QOL) and select the optimal approach for the objective of extending healthy lifespans in order to form a society of health and longevity.

9. Miscellaneous

For this Objective, there are a number of previous Research and Development Objectives that are relevant: (1) the FY2012 Research and Development Objective "Integrated clarification of the maintenance and change mechanisms of dynamic homeostasis in the body and creation of technology to understand and regulate complex dynamic homeostasis to achieve preventive medicine, appropriate diagnosis and treatment;" (2) the FY2012 Research and Development Objective "Creation of new technologies for breakthrough in understanding and predicting biological activities and intermolecular interactions by means of "Novel Structural Life Science" that contributes to new medical treatment and prevention of various diseases, food safety enhancement and environment improvement," and (3) the Innovative Area "Integrative Understanding of biological phenomena with temperature as the key theme." It is expected that the results from these programs will suggest research themes to be developed in this research.

To pursue this Objective, an active approach to mutual collaboration is planned with Moonshot Goal #2 "Realization of ultra-early disease prediction and intervention by 2050" in the Moonshot Research and Development Program, AMED's Strategic Research Program for Brain Sciences (SRPBS), Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS), and the Strategic International Brain Science Research Promotion Program.

JST and AMED are simultaneously releasing their own strategic fields under this common objective, in a first attempt to further strengthen their collaboration through research. It is hoped that this will allow effective progress in developing an integrated understanding of human multi-sensory networks and clarifying their control mechanisms, as well as strengthening the connections between researchers, providing a step up for young researchers, and simplifying/improving the convenience of applications and other administrative processes. We hope that this will lay the foundation for this field of research in Japan and rapidly develop connections between companies.

Furthermore, in light of the trends at various countries overseas, we expect research to progress in an efficient and effective manner through this proactive approach to promote joint research between a wide array of researchers in Japan and overseas.

15.5 New approaches in drug and vaccine discovery for infectious diseases

1. Objective Title

New approaches in drug and vaccine discovery for infectious diseases

2. Overview

During the course of the COVID-19 pandemic, Japan has lagged behind in the development of vaccines and therapeutics. In order to respond with immediacy in future pandemics, the research process will need to be accelerated with in-depth understanding of the host-pathogen interactions, from basic discovery of a drug or vaccine to its pre-clinical and clinical development. However, several issues peculiar to Japan have hindered this process, including the lack of continuous investment in research and development, shortage of investigators engaged in drug discovery, insufficient collaboration across relevant research disciplines, declining overall interest in therapeutic applications, and the withdrawal of pharmaceutical companies from infectious disease research. Furthermore, the process of basic research has become the bottleneck for drug discovery due to the diversity of pathogens, various phases of disease from acute to chronic and latent infections, and the necessity to respond immediately during a pandemic, which are problems that are unique in infectious diseases.

In order to break through this impasse, this research and development program aims to establish the infrastructure and modalities that will promote basic research towards innovative drug discovery. Specifically, the project aims to promote interdisciplinary research through organic collaboration among domestic and overseas research institutions, industry, and other stakeholders and generation of new research and development methodologies in the field of infectious disease drug development. This will entail effective utilization of domestic infectious disease research hubs, as represented by the BSL4 facility at Nagasaki University, and various research resources (cryoelectron microscopes, in silico analysis, the supercomputer Fugaku, etc.), as well as the active participation of early career investigators in various fields not limited to infectious diseases and microbiology.

3. Goals and Objectives

This Research and Development Objective aims to resolve issues that are the rate-limiting steps in drug discovery research, by building or repurposing drug discovery infrastructure and modalities for infectious disease drug discovery research and developing strategies that ultimately translate to clinical application, as well as strongly promoting interdisciplinary basic research. This Objective aims to achieve three specific goals:

(1) Development of drug discovery modalities that will contribute to the prevention and treatment of infectious diseases

(2) Optimization of existing modalities for infectious disease drug discovery

(3) Generation of technology platforms that will accelerate infectious disease drug discovery leading to innovative preventive and therapeutic agents against infectious diseases

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

Achieving the goals outlined in section 3. Goals and Objectives will help our society achieve the vision outlined below through the continuous execution of infectious disease research with a focus on the basic phases that facilitate development of therapeutics.

- Build up a body of research that contributes to faster drug discovery, so that these research outcomes can be leveraged to allow faster development of preventive and therapeutic agents when a new infectious disease emerges.
- Generate and maintain a robust network of investigators and drug discovery research platforms in place that enables an immediate response when an infectious disease starts to spread.

5. Specific Research Examples

The expectation is for research that interconnects or combines the following elements from (1) to (3):

(1) Development of drug discovery modalities that will contribute to the prevention and treatment of infectious diseases

The objective is to develop novel drug discovery modalities that contribute to the prevention and/or treatment of infectious diseases, based on promising seeds created from prior basic research, such as knowledge of essential pathogen characteristics or the mechanisms involved in disease manifestation.

- Basic research that may lead to development of new preventive and/or therapeutic agents, based on findings on the pathogenesis in the body, interactions with intracellular organelles, and the pathway by which infection is established including proliferation within the cells.
- Establishment of novel therapeutic concepts and development of modalities through elucidation of epigenetic modulation of pathogen proliferation, the role of the microbiome, and the host defense mechanism.
- Exploratory research aimed at the development of novel antimicrobials (small molecules, natural substances, other modalities) that target the virulence factors, such as control of the bacterial toxin secretion system or quorum sensing transcription factors.

(2) Optimization of existing modalities for use in infectious disease drug discovery

The objective is to search for new approaches to infectious disease prevention and treatment by applying modalities from research and development that has already progressed in disease areas other than infectious diseases and optimizing these modalities for infectious diseases.

- Generation of technology platforms for application in antiviral drug discovery, including nucleic acid therapeutics, peptides, nanobodies, and compounds that induce targeted protein degradation.
- Development of research platforms aimed at understanding the mechanism of drug resistance and development of pharmaceutical agents to inhibit or counter relevant mechanisms of resistance.
- Exploratory research to build infrastructure to search for innovative protective antigens against pathogens for which no effective vaccines are currently available or more effective vaccines are needed and to develop suitable vaccine modalities

(3) Development of technology platforms that will accelerate discovery of innovative preventive and therapeutic agents against infectious diseases

The objective is to contribute to acceleration in the research processes, by transforming methods and resources being utilized in infectious disease drug discovery and optimizing these methods/resources.

- Development of infectious disease animal models that can be used for clinical prediction, not limited to primates and rodents, but also models that are humanized, such as humanized mice, chimeras, and human tissues of iPS cell origin.
- Refinement of in silico screening using structural analysis and protein science which facilitates rational drug design for compound optimization and complements wet studies.
- Development of an infectious disease drug discovery AI platform using big data that can draw on Reverse Translational Research (rTR), multi-omics analysis, and other relevant areas.
- Development of analytical methods using biostatistics and biomathematics and the development of platform technologies for prevalence prediction, through the use of databases on pathogen evolution and genome mutations to identify pathogen immune evasion mechanisms, optimization of natural host symbiosis, and prediction of the emergence of variants or resistant strains. Also, development of modalities to enable immediate response.

6. Domestic and International Research Trends

In terms of basic research in the infectious diseases field, under the Japan Agency for Medical Research and Development (AMED)-supported Japan Initiative for Global Research Network on Infectious Diseases (J-GRID) and Japanese Initiative for Progress of Research on Infectious Disease for global Epidemic (J-PRIDE), as well as two programs taken over by the Japan Program for Infectious Diseases Research and Infrastructure, research has been underway long-term in Japan and overseas regions where infectious diseases are prevalent with the goal of developing an understanding of epidemiology and the essential nature of pathogens and exploring drug discovery targets and mechanisms of pathogenesis. Work is also underway at RIKEN, the AMED project Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS), and the National BioResource Project (NBRP) to install and upgrade advanced technology and research infrastructure to contribute to the aforementioned research domains, including AI drug discovery, human organoids, large-scale compound libraries, high-throughput screening (HTS), and structural analysis using cryoelectron microscopy.

Domestic trends

In terms of fields relevant to this Research and Development Objective, there have been examples to date of basic research in the CREST research area “Translational Research for Intractable Immune Disorders and Infectious Diseases” that is relevant, from the perspective of infection and immunity, to the development of new vaccines and drugs against the bacteria, parasites, and viruses that cause infectious diseases such as tuberculosis, malaria, or AIDS. In addition, in the ERATO project “KAWAOKA Infection-induced Host Responses” and in the MEXT Scientific Research on Innovative Area programs “Molecular basis of host cell competency in virus infection” and “Neo-virology: the raison d'etre of viruses”, research has targeted the mechanisms of host-pathogen interactions, as well as the essential nature of viruses. This Research and Development Objective is defined to leverage the aforementioned ongoing research programs, as well as basic and fundamental research outcomes on infectious disease drug discovery originating from the Japan Program for Infectious Diseases Research and Infrastructure.

International trends

In Europe and the US, basic research has been underway in various fields related to infectious diseases, including the mechanisms by which microorganisms express their pathogenicity and the immune response to infection. Unlike in Japan, the US and Europe have substantial support systems and competitive funding mechanisms in place to help funnel the findings originating from basic research into subsequent applied research and clinical development. Furthermore, during the recent development of vaccines against the novel coronavirus, modalities that had been already under development for other diseases were quickly applied for infectious diseases, which enabled rapid vaccine roll-out.

In China, the spread of SARS (2002–03) and MERS (2015) in the country was a strong motivating force behind the development of national policy on infectious disease research, which has resulted in a wide range of research findings in the virology field, particularly around influenza.

7. History of the Investigations

A review of the research field was conducted as described below, based on the Policy on Defining Strategy Targets (decision dated July 2019 by the Council for Science and Technology, Basic Research Promotion Subcommittee).

(1) Research trends in Japan were analyzed using the Grants-in-Aid for Scientific Research (Kakenhi) database and other sources as well as a database on research papers. The findings were used to generate a questionnaire-based survey of key research trends that was disseminated 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 Center for Research and Development Strategy (CRDS) of Japan Science and Technology Agency (JST), and the Program Directors at AMED.

(2) As a result of further analysis with reference to the above questionnaire-based survey results and expert briefings, it was recognized that, although basic research comparable to that in various other countries has been conducted thus far in the field of infectious diseases, the findings generated by basic research rarely progressed into applied research or was out-licensed to pharmaceutical companies and other organizations, due to various factors including fragmentation of expertise across multiple pathogens and a lack of interdisciplinary research networks, and also the withdrawal from the infectious disease drug discovery business by Japanese pharmaceutical companies. " New approaches in drug and vaccine discovery for infectious disease" was therefore defined as a research field of interest.

(3) In November 2020, the Ministry of Education, Culture, Sports, Science and Technology (MEXT) in collaboration with AMED held a workshop to bring together experts in this research field from industry and academia. The workshop discussed the current status of and challenges in basic research into infectious disease drug discovery; the direction of R&D to achieve breakthroughs (new trends) in infectious disease drug discovery research and the outcomes that need to be achieved during the research period; and the scientific value that could be created in the future as well as social and economic impacts.

In light of the above, AMED has defined "New approaches in drug and vaccine discovery for infectious diseases" as a Research and Development Objective in order to promote the fusion of research from different fields and further accelerate infectious disease drug discovery research.

8. Relevant Descriptions Included in Japanese Cabinet Documents

The Healthcare Policy (Cabinet decision dated 27 March 2020)

4.1. (1)

- Regarding the disease area described above that is a social issue for Japan today and in the future, research and development will be promoted on various themes including those described below.

  (Text omitted)

- Share information on various pathogens in Japan and overseas, including genomic information, and pursue international risk assessments regarding infectious diseases; conduct research and development into diagnostics, therapeutics, and vaccines, etc. against infectious diseases, including new viruses like the novel coronavirus; and build research and development platforms that allow an immediate response when an emerging infectious disease starts to spread.

4.1. (2)

- In order to recruit and train experts in pathogen handling and to improve basic research capabilities in infectious diseases at research institutions in Japan, the necessary support will be provided for the establishment of BSL4 facilities etc. and connections will be strengthened between state, university, and local government regional public health laboratories, etc. To strengthen biosecurity as well as implement pandemic countermeasures, Japan will work to increase the nation's crisis management capabilities, with reference to systems at the Centers for Disease Control and Prevention (CDC) in the US and elsewhere, and will also develop a system for rapid research and development to tackle problems in an emergency.

Basic Policy on Economic and Fiscal Management and Reform 2020 (Cabinet decision dated 17 July 2020)

3. (2)

The government and the private sector will promote strategic and high-quality research and development […] by focusing on […] countermeasures against infectious disease […] including research and development of effective therapeutics, medications and vaccines.

Integrated Innovation Strategy 2020 (Cabinet decision dated 17 July 2020)

Part I. 4. (1)

As a matter of urgency, Japan needs to strengthen the nation's ability to respond to emerging or re-emerging infectious diseases, now and in the future, and will work to improve the nation's infectious diseases response through international information sharing and the development of pharmaceuticals and medical devices to manage infectious diseases.

Part I. Chapter 2. 1. (2)

(Text omitted)

Through an industry-academia-government partnership, Japan will pursue research and development to create innovative pharmaceuticals and medical devices, etc., including measures against novel coronavirus infections.

Part I. Chapter 2. 1. (4)

(Text omitted)

○ Japan aims to support research at infectious disease research sites, mainly BSL4 facilities; conduct epidemiological studies in regions where disease is prevalent; conduct basic research that will contribute to prevention, diagnosis, and treatment; and pursue strategic international joint research in the fields of humanities and social sciences as well. Japan also aims to accumulate and utilize clinical and epidemiological data, etc. to prepare for future outbreaks, conduct basic research that can contribute to future infectious disease countermeasures from a mid- to long-term perspective, and expand the research infrastructure to support this research.

Part I. Chapter 2. 1. (5)

○ In order to improve Japan's basic research capabilities in infectious diseases and recruit and train human resources, the necessary support will be provided for the establishment of BSL4 facilities and connections will be strengthened between relevant institutions. In addition, Japan will work to increase the nation's crisis management capabilities, with reference to systems at the CDC in the US and elsewhere, and will also develop a system for rapid research and development of emergency pharmaceuticals and medical devices, etc. to tackle problems in a crisis.

Bio-Strategy 2020 (Decision of Council for Integrated Innovation Strategy dated 26 June 2020)

4

(Text omitted) For emerging infectious diseases such as the novel coronavirus, rapidly implement initiatives for the development of diagnostic methods, therapeutic methods, vaccines, and devices and systems

4.1.1 ①

- Selection of candidate therapeutic agents using in silico analysis, development of antiviral agents
- Investigations into therapeutic efficacy and safety of therapeutic agents

4.1.1 ②

- Development of rapid test devices
- Real-world experimental research on new rapid detection methods

4.1.1 ③

- Pursuit of research and development to create innovative pharmaceuticals and medical devices, etc., including measures against novel coronavirus infections through an industry-academia-government partnership

4.1.1 ④

- Research projects for the development of diagnostic and therapeutic methods, etc. that reflect new research trends and for surveillance to inform responses to subsequent waves of infection
- Development of new technology platforms for research and development into emerging infectious diseases
- Wide-ranging call for potential new technology platforms needed for research and development into drug discovery, etc. for emerging infectious diseases including the novel coronavirus

4.1.2

- Establishing analytical infrastructure for pathogens and infectious clinical specimens, etc., and expand drug discovery infrastructure in the infectious disease area
- Strengthening support for drug discovery research and pursue basic research at infectious disease research

sites overseas

- Establishing systems for the rapid development of therapeutic agents to treat novel coronavirus infections

9. Miscellaneous

To make progress with this Research and Development Objective, we expect research to be executed in an efficient and effective manner through a proactive approach to collaborations with (1) basic research by the Japan Program for Infectious Diseases Research and Infrastructure; (2) the outcomes originating from research relating to various types of resource handling technologies, imaging, developmental biology, genomics, and immunology undertaken by RIKEN; and (3) various types of technologies and platforms that will accelerate drug discovery research currently being supported by the AMED project Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS) and the National BioResource Project (NBRP).

In addition, in light of the future increase in activity in the infectious disease research fields, when submitting a research proposal, proposals where early career investigators take the leading role and proposals designed to have links with overseas institutions that conduct cutting-edge research are encouraged. Furthermore, it is expected that the results generated from the research conducted under this Research and Development Objective will be built up as a body of research that can be immediately leveraged in the case of a new infectious disease epidemic in the future, and will also lead to practical applications via out-licensing to pharmaceutical companies or research bodies run by AMED to promote the development of innovative pharmaceuticals against emerging or re-emerging infectious diseases.

Division of Innovative Research and Development
Department of Innovation and Clinical Research Center

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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