FY2021

Advanced Research and Development Programs for Medical Innovation (Term 1; AMED-CREST, PRIME)

Application Guidelines

March 2021

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").

Notice: this application guidelines describes about ONLY the Existing Research Areas (Term 1). There are two terms of FY2021 application depending on Research Areas; Term 1 solicits for Existing Research Areas and Term 2 does for New Research Areas. Please refer to "the Application Guidelines for Term 2" publish by the middle of April. Due to simultaneously applying for both the Term 1 and the Term 2 is not allowed, the term 1 program applicants will not be able to apply the Term 2 Research Areas, and vice versa.

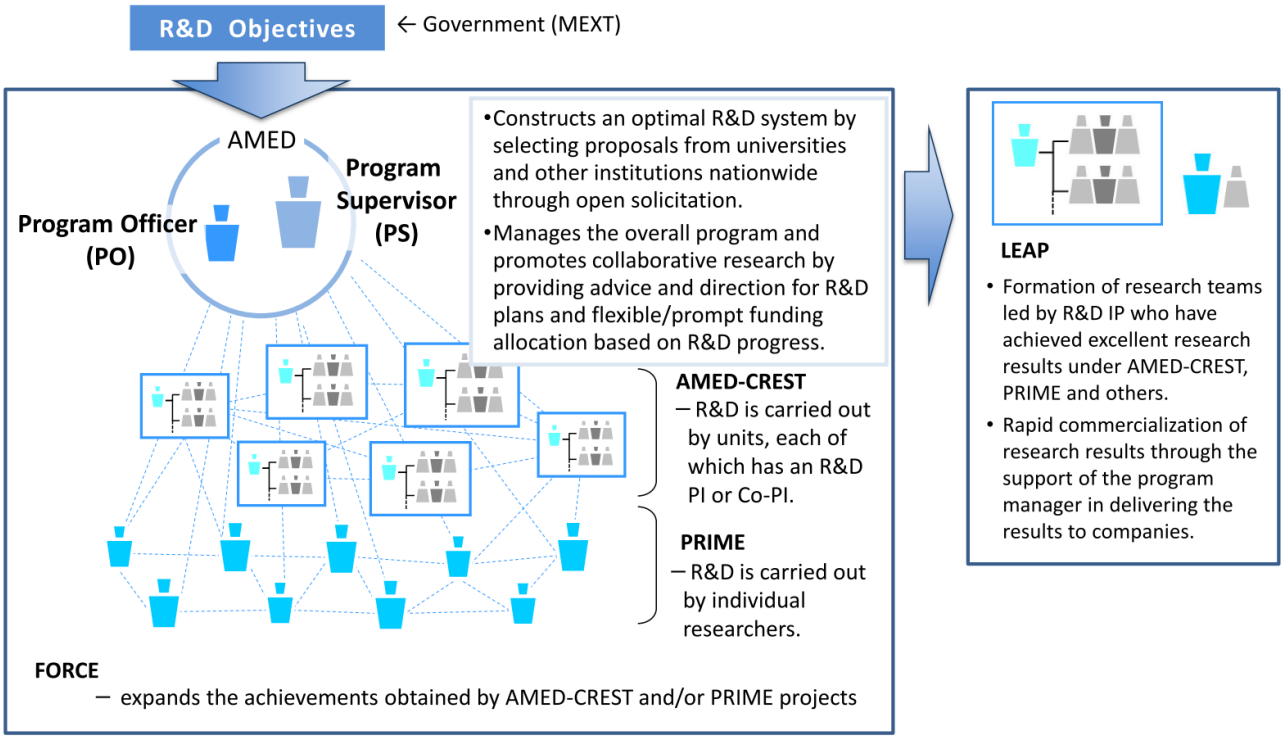
1.1 Program Outline

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 and PRIME 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 R&D Period and R&D Costs

The general R&D period and budget for one R&D project are shown below. In some cases, budget ranges may be set independently for individual R&D areas. Please 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, Program Officers, and R&D Area Advisors 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, etc. 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 areas of disease (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 projects 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

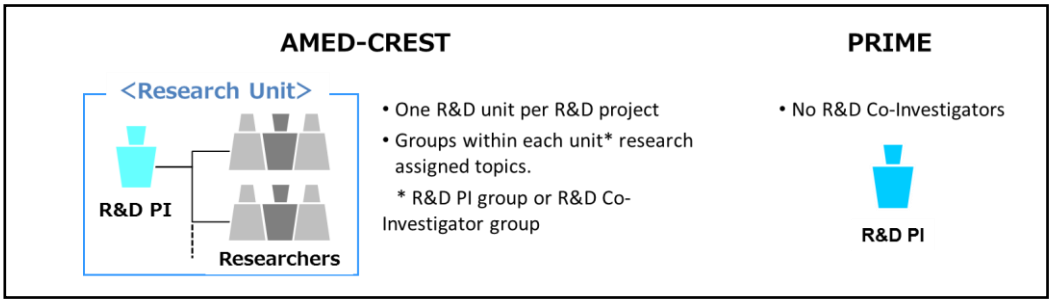
1.2.2 R&D Unit Organization

(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 and that is their main place of research;[1] which has concluded a direct contracted R&D agreement with AMED;[2] and which is the research institution, etc., in Japan referred to in Chapter 2.

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

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

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

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

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

[2] For details regarding contracted R&D agreements with institutions under this program, please refer to Chapter 8.

Chapter 2. Application Requirements

2.1 Eligible Applicants

Eligible Applicants for this program shall be researchers 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 ("R&D Principal Investigator" (PI)).

(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 special private corporation, general incorporated association, general incorporated foundation, public interest incorporated association, or public interest incorporated foundation (hereinafter referred to as a "special private corporation, etc.") whose main activity purpose is research.

(F) An independent administrative 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) Non-profit, charitable technology research associations[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] With regard to technologies used in industrial activities, mutual associations providing finance, human resources, and facilities in which the association members autonomously conduct joint research.

(2) In the case that the project is selected, the research 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.) 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, 2021. However, in the case that the above conditions are not met by October 1, 2021, 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.

(4) When 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 in question (The approval of the Program Supervisor is required.).*
- The overseas research institution is required to transfer, free of charge, intellectual property rights to the Principal Institution. (Article 19 of the Industrial Technology Enhancement Act (Act No. 44 of 2000) (Japanese version of the Bayh-Dole Act) does not apply to overseas research institutions.)
- The overseas institution must be able to properly execute the budget in accordance with the R&D agreement or AMED's budget execution policy if such has been specified by AMED, and must be able to submit a detailed statement of R&D expenses to AMED (equivalent to the balance book of Japanese institutions) prepared in English.
- Payments to the overseas research institution for indirect costs must not exceed 30% of the direct costs.

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

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 FY2021 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 FY2021, each applicant may submit an application for only one R&D or research area.

* 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 (i), 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 FY2021, 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-I (acceleration phase) 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) Individual Researchers of ACT-X under the JST Strategic Basic Research Programs (Creating New Technological Seeds)

(i) 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) One cannot 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, one cannot simultaneously perform the role of Individual Researcher for a

PRESTO, ACT-X or ACT-I (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. These limitations do not apply if the applicant's ongoing research project is due to conclude in FY2021. 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 not possible for an R&D PI for a PRIME project or an Individual Researcher for a PRESTO, ACT-X, or ACT-I (acceleration phase) project to be appointed as a Co-investigator for an AMED-CREST project proposal (unless the research period for the PRIME, PRESTO, ACT-X or ACT-I (acceleration phase) project is due to conclude in FY2021.).

(b) If an applicant applies to PRIME and their PRIME project proposal and a 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, AMED and JST shall make adjustments so the applicant reconsiders their role in the AMED-CREST/CREST project (although they may not participate as the Co-Investigator or Lead Joint Researcher, it is possible for the applicant to participate as a project participant, or Research Participant/other Research Participant), or withdraws the proposal for PRIME.

(c) An applicant who currently holds the position of Co-investigator for an AMED-CREST, FORCE, or LEAP project, Lead Joint Researcher of a CREST project, or Group Leader of a ERATO project may apply to PRIME, but if the applicant is shortlisted as candidates, AMED and JST shall make adjustments so that the applicant reconsiders their role in the AMED-CREST, FORCE, LEAP, CREST, or ERATP project (although they may not participate as the Co-Investigator, Lead Joint Researcher, or Group Leader, it is possible for the applicant to participate as a project participant, or Research Participant/other Research Participant), or withdraws the proposal for PRIME.

(5) Those who are planning to submit an application for LEAP for FY2021 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.

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, ACT-I (acceleration phase), ERATO), unless the research period for your project ends within FY2021.

Position in research proposal / Current position in ongoing research project		AMED-CREST (AMED)			PRIME (AMED)
		R&D PI	Co-Investigator	Project participant	R&D PI
	R&D PI	Not eligible	Eligible[1]	Eligible[1]	Not eligible[4]

AMED-CREST (AMED)	Co-Investigator	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[2]
	Project participant	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1]
PRIME (AMED)	R&D PI	Not eligible[4]	Not eligible	Eligible[1]	Not eligible
FORCE (AMED)	R&D PI	Not eligible[4]	Eligible[1]	Eligible[1]	Not eligible[4]
	Co-Investigator	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[2]
	Project participant	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1]
LEAP (AMED)	R&D PI	Not eligible[4]	Eligible[1]	Eligible[1]	Not eligible[4]
	Co-Investigator	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[2]
	Project participant	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1]
CREST (JST)	Research Director	Not eligible[4]	Eligible[1]	Eligible[1]	Not eligible[4]
	Lead Joint Researcher	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[2]
	Other Research Participant	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1]
PRESTO (JST)	Individual Researcher	Not eligible[4]	Not eligible	Eligible[1]	Not eligible[4]
ACT-X (JST)	Individual Researcher	Eligible[3]	Not eligible	Eligible[1]	Eligible[3]
AIP Acceleration Research (JST)	Research Director	Not eligible[4]	Eligible[1]	Eligible[1]	Not eligible[4]
	Collaborator	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[2]
	Other Research Participant	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1]
ACT-I (acceleration phase) (JST)	Individual Researcher	Not eligible[4]	Not eligible	Eligible[1]	Not eligible[4]
ERATO (JST)	Research Director	Not eligible[4]	Eligible[1]	Eligible[1]	Not eligible[4]
	Co-Research Director	Not eligible[4]	Eligible[1]	Eligible[1]	Not eligible[4]
	Group Leader	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[2]
	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] If the applicant is shortlisted as a candidate for PRIME, AMED and JST shall make adjustments so that the applicant reconsiders their role in the AMED-CREST, FORCE, LEAP, CREST, AIP Acceleration Research, or ERATO project (although they may not participate as the Co-Investigator or Lead Joint Researcher, it is possible for the applicant to participate as a project participant, or Research Participant/other Research Participant), or withdraws the proposal for PRIME.

[3] 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.

[4] 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.)

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, ACT-I (acceleration phase), 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[2]
	Project participant	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1]
PRIME (AMED)	R&D PI	Not eligible	Eligible[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[2]
	Project participant	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[1]
CREST (JST)	Research Director	Not eligible	Eligible[1]	Eligible[1]	Not eligible
	Lead Joint Researcher	Eligible[1]	Eligible[1]	Eligible[1]	Eligible[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[2]	Eligible[1]	Not eligible
PRESTO (JST)	Proposal subject to the Feasibility Study of Specific Research Proposal in the previous fiscal year	Not eligible	Eligible[2]	Eligible[1]	Not eligible
ACT-X (JST)	Individual Researcher	Not eligible	Eligible[2]	Eligible[1]	Not eligible

[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] If both research proposals 1 and 2 are both shortlisted as candidates, AMED and JST shall make adjustments so that the applicant reconsiders their role in the AMED-CREST, LEAP, or CREST project (although they may not participate as the Co-Investigator or Lead Joint Researcher, it is possible for the applicant to participate as a project participant, or Research Participant/other Research Participant), or withdraws the proposal for PRIME, PRESTO, or ACT-X.

[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.

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 research achievements and accounting reports). In submitting an application, please be sure to carefully read the program outline, the outline of R&D projects for which applications are being solicited, and other information provided and thoroughly consider the kinds of results your proposed R&D project can produce before completing the proposal documents. For details, please refer to Chapter 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) or outside of Japan, permission must be received in advance. "Provision of technology" includes not only the provision of blueprints/designs, specifications, manuals, samples, prototypes, and other technological information via paper, e-mail, CD, DVD, USB flash drive, or other storage medium but also the provision of operational knowledge through technological guidance or skills training and technological support at seminars, etc. There are cases in which large amounts of technological exchange that could be subject to regulation under the Foreign Exchange Act may be included in joint research activities or when international students are involved.

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

- Ministry of Economy, Trade and Industry: Security Trade Control (general)
  https://www.meti.go.jp/policy/anpo/
- Ministry of Economy, Trade and Industry: Handbook for Security Trade Control
  https://www.meti.go.jp/policy/anpo/seminer/shiryo/handbook.pdf
- Center for Information on Security Trade Control
  https://www.cistec.or.jp/
- 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

2.5.4 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.

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 (agreed on February 12, 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)

2.5.5 Data Sharing

With regard to the treatment of data arising from the results 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 is made obligatory; the AMED Guidelines Concerning Utilization of Research Data* that compile the definition of R&D data, policy regarding the treatment etc. of R&D data, and specific management guidelines have also been formulated, and are available on the AMED website. For the details regarding submission of data management plans, please refer to Chapter 7.

Furthermore, the contracted R&D agreements applied in common to all contracted R&D that uses AMED's public funding in principle forbid the disclosure or provision to third parties of any type of R&D data generated, acquired or collected. However, in cases in which it is permitted according to guidelines already published by AMED, 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 designated as either unrestricted release data or restricted release data, and is required to be published. Furthermore, even if certain data falls under the categories of either unrestricted release

data or restricted release data it is permitted to share it only with specific third parties for the duration of the period when it is treated as restricted sharing data prior to release. For further details please refer to the AMED Guidelines Concerning Utilization of Research Data.*

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

Chapter 3. R&D Projects Being Solicited

The Term 1 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[2])	Period in which R&D is Scheduled to be Implemented	Planned Number of New Awarded Projects
1	Understanding proteostasis and discovering innovative medical applications (PS: Kazuhiro Nagata) (PO: Tamao Endo)	AMED-CREST[1]	Max. of 260 million yen for total R&D period for each project	Max. of 5.5 years FY2021– FY2026	Around 3–5 projects
		PRIME	Max. of 40 million yen for total R&D period for each project	Max. of 3.5 years FY2021– FY2024	Around 8–12 projects
2	Understanding of the biological phenomena and responses at the early life stages to improve the quality of health and medical care[3] (PS: Hiroyuki Sasaki) (PO: Hiroyuki Takeda)	AMED-CREST[1]	Max. of 300 million yen for total R&D period for each project	Max. of 5.5 years FY2021– FY2026	Around 2–4 projects
		PRIME	Max. of 40 million yen for total R&D period for each project	Max. of 3.5 years FY2021– FY2024	Around 8–12 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] When a proposal is submitted for AMED-CREST research, AMED Reviewers affiliated with the overseas research institution will be added to the screening process, so the R&D proposal to be submitted should be partly prepared in English.

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

[3] The 2021 solicitation will be the final call for proposals.

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

3.2.1 Understanding proteostasis and discovering innovative medical applications

Program Supervisor (PS): Kazuhiro Nagata, Director General, JT Biohistory Research Hall

Program Officer (PO): Tamao Endo, Senior Fellow, Tokyo Metropolitan Institute of Gerontology

* R&D Area for the Research and Development Objective “Understanding and medical application of proteostasis” (page 82)

Outline of the Research and Development Area

Recent developments in genome sequencing technologies have led to a greater understanding of the relationship between genetic mutations and a wide range of diseases, but there are still numerous diseases for which the molecular pathways leading to disease onset are unclear. In numerous cohort studies, researchers have observed cases where the disease-related genes are present, but the disease does not necessarily occur. In future disease research, we need to expand our focus beyond analysis at the level of expression from gene to protein, and deepen our understanding of the processes involved in posttranslational modifications (e.g., glycosylation, oxidation, glycation) and earlier translation control mechanisms. However, compared with research into nucleic acids, which are easy to handle because of their comparatively simple structures, research into proteins has been slow to get off the ground, reflecting the complex molecular sequences and structural diversity of proteins, as well as the ability of proteins to change structure and function in line with the surrounding environment, all the while being subject to posttranslational modifications. Even for proteins identified as having a direct relationship with disease, there are few examples where there are substantiated answers to questions such as what types of structural changes are important, how are these structural changes recognized by the body, and how does this relate to disease onset? To clarify how various posttranslational modifications like glycosylation affect protein structure and quality control, as well as how this physiological function is controlled, we need to focus on proteostasis and subsequent posttranslational modifications. We need to make this research area more internationally competitive by identifying the molecular mechanisms leading to disease.

This R&D area aims to clarify the relationship between structure and function based on evidence obtained from biochemical and structural biological approaches, to understand the molecular pathways that cause various diseases, and to discover potential solutions for healthcare or methods to maintain good health. The R&D is focused on understanding the molecular basis of proteins during the processes that occur between initial protein translation and synthesis to ultimate degradation, and will investigate denaturation, aggregation, and degradation reactions that set proteins on a final, irreversible pathway, as well as posttranslational modifications that have irreversible effects on protein function. Target diseases include, but are not limited to, neurodegenerative disease, mental health disorders, intractable cancers, chronic inflammatory diseases, amyloidosis, fibrosis, rare diseases, infectious diseases, and lifestyle diseases like arteriosclerosis and diabetes, as well as insights into how to avoid aging and maintain a healthy state. As well as researchers involved in the fields of proteins and glycans, we welcome participation by basic science or clinical researchers in structural biology, immunity, metabolism, or nerve systems, as well as researchers from other fields, including analytical chemistry and bioinformatics. The goal is to make progress in world-class, highly innovative research and development by bringing together and leveraging the strengths of a range of disciplines.

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

The objectives for projects in this R&D area are to identify dynamic structural changes in proteins using novel concepts, further our understanding of the molecular mechanisms that lead to functional change and disease onset, and link this to the discovery of potential healthcare solutions for the future. For posttranslational modifications, the focus is on glycosylation that produces complex modified forms without direct regulation of gene expression; more conventional non-enzymatic modification reactions such as glycation, oxidation, nitration, and polysulfidation; and also unknown modification reactions. However, we will not accept proposals for the following types of research: (1) research into systems that use reversible protein modification to effect functional change, such as phosphorylation and lipid oxidation affecting protein localization with the objective of understanding signaling systems or (2) research that mainly concerns the development of a functional understanding of substances (e.g., membrane lipids, nucleic acids) other than those involved in the protein itself or posttranslational modifications.

Note that in terms of the management of research in this field, the plan is to link with research fields at the Japan Science and Technology Agency (JST), implemented under the strategic target "Understanding proteostasis and medical applications" as decided by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) for this time period. With an eye on future R&D development, we will actively develop networks through collaboration between research groups.

(1) AMED-CREST (unit-type)

For this R&D area, we invite proposals for innovative basic research that takes a transdisciplinary approach with the goal of understanding protein denaturation, regeneration, aggregation, and degradation processes, in terms of an understanding of normal maturation processes and the relationship with disease. We expect posttranslational modifications such as glycans to be a major focus for projects in this R&D area, as such modifications play a role in the control of protein structure, functional change, and degradation.

Below we provide examples of anticipated R&D proposals, but we are looking for world-class, innovative research proposals that go beyond these examples. We hope for original proposals that go beyond current frameworks and use new concepts to drive a paradigm shift in the fields of the life sciences and disease research.

- Understand the early-stage processes occurring in vivo, including protein denaturation and aggregation, and the molecular mechanisms of the processes involved in progression (including environmental factors, positional information, and posttranslational modifications); also understand control mechanisms due to constituent elements in vivo (e.g., regeneration, disaggregation and degradation).
- Identify the mechanisms involved in the recognition and response to denatured/aggregated proteins (abnormal proteins) and abnormal modifications in vivo or molecule species that exhibit cytotoxicity, and understand the mechanisms of disease onset, such as analysis of the molecular mechanisms that manifest as toxicity.
- Conduct biochemical and structural biological analyses of abnormal proteins and posttranslational modifications in human disease tissues and how they relate to location information, and use these findings to develop highly extrapolative experimental models.

- Develop technology to detect at a high sensitivity the presence and location of abnormal proteins and special posttranslational modifications in biological tissues.
- Create technologies to control (e.g., suppress toxicity, promote degradation) the synthesis and spread of abnormal proteins as described above.
- Create mathematical models using bioinformatics methodologies that can model and predict the molecular mechanisms leading to disease onset, in light of biochemical and molecular biological evidence on protein denaturation/aggregation and posttranslational modifications.
- Understand the mechanisms behind abnormal protein synthesis based on abnormalities in the protein translation mechanism and understand the molecular mechanisms involved when these abnormal proteins affect cells and tissues in the body.
- For proteins in cell surface receptors and adhesion molecules, as well as in extracellular matrix domains, understand the mechanisms of disease onset based on proteome analysis and analysis of the correlation between structure and function, as well as control mechanisms regulating protein physiological functions that involve glycans or changes in site-specific glycosylation.
- Discover cell engineering and chemical technologies that enable control of site-specific glycan structures and control of the nonuniformity of glycosylation.
- Understand the environmental factors, biochemical structural changes, and molecular pathways involved in glycation, oxidation, and other modifications, and analyze functional changes in modified proteins.

When submitting an application, the following points should be noted when drafting the research proposal.

- Applicants are asked to hypothesize on at least one disease relevant to the target proteins or phenomena under research or the process of posttranslational modification. When the application is submitted, **it is not necessarily** to include proof of the connection, but the research proposal should include how the research will clarify the relationship to disease and develop an understanding of molecular mechanisms that could provide potential new healthcare solutions. Ideally, the research would progress to comparative investigations into whether findings from cultured cells and model organisms are actually applicable to human disease.
- **There is no requirement** for a single team to investigate an understanding of all three items of protein denaturation, aggregation, and degradation. **There is also no requirement** for a single team to investigate both proteins and posttranslational modifications like glycosylation.
- When using human samples, the research proposal should clearly describe regulatory compliance, for example with ethics submissions, and sample collection methods.
- When submitting the proposal, **there is no need** to include participation by multiple researchers from different fields in a single team, but the proposer should consider building the essential team needed to prove a new concept. In terms of a multidisciplinary approach, as discussed above, during the research implementation phase, intra- and interdisciplinary interactions should be factored in as necessary, alongside a proactive approach to information sharing and exchange of opinions.

When implementing research in this area, we welcome innovative proposals from various different fields of research in order to ensure substantial networks are formed as discussed above. Hypotheses should be developed that link discoveries in new life sciences research and disease research, with plans to prove these hypotheses in a logical fashion.

We will select approximately 3–5 proposals for AMED-CREST this fiscal year, with a total budget of up to 260 million yen per project for R&D costs (direct costs) over the project term.

(2) PRIME (solo-type)

The PRIME program involves research performed by an individual researcher 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 ambitious programs that could overturn existing concepts, challenging programs that could generate unique research leading to new breakthroughs, or research to develop novel technologies that may contribute to basic research in this R&D area, with a particular focus on abnormal proteins and posttranslational modifications.

Under the PRIME program, researchers are not necessarily expected to produce evidence at the end of the research period demonstrating links to disease. We expect proposals for challenging programs that might prompt a paradigm shift in disease research in the future.

Looking ahead to the future development of their research, 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. By building networks in this way, this program will support proposers to progress their career and become world-class medical and basic science researchers.

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 will consider proposals from researchers not currently involved in protein research if they present ideas in this research area involving new concepts or analytical methods. We support the formation of networks for the implementation of research in this area, so that the researcher can achieve the research proposal and make further progress. Proposals should be feasible to implement, with a proactive approach taken to scientific rationality and describable new hypotheses.

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

Briefing of Solicitation

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_00003.html

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

Program Supervisor (PS): Hiroyuki Sasaki, Distinguished Professor, Medical Institute of Bioregulation, Kyushu University

Program Officer (PO): Hiroyuki Takeda, Professor, Graduate School of Science, the University of Tokyo

* R&D Area for the Research and Development Objective "Molecular understanding of the biological phenomena and responses at the early life stages to improve the quality of health and medical care" (page 86)

Outline of the Research and Development Area

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

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

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

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

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

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

(1) AMED-CREST (unit type)

For this R&D area, we invite proposals for innovative basic research in which researchers adopt a multidisciplinary approach to qualitatively understand the biological phenomena and responses at the early stages of life and clarify the mechanisms involved. We also invite proposals for research into biomarkers to evaluate biological responses or the discovery of platform technology seeds for the regulation of these responses.

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

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

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

- Develop technologies for the precise control of epigenomic status or protein functions that are potential interventional targets

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

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

(2) PRIME (solo type)

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

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

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

Briefing of Solicitation

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_00003.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 of the Term 1 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 11.)	
Period of acceptance of proposal documents	**It should be noted that the period of acceptance of proposal documents varies from one R&D area to another** **<Understanding proteostasis and discovering innovative medical applications>** **<Understanding of the biological phenomena and responses at the early life stages to improve the quality of health and medical care>** **From Tuesday, March 23rd, 2021 to Tuesday, May 11th, 2021 at noon (JST) (Observe strictly)**
Document review	**Late June 2021 to the middle of July 2021 (tentative)**
Interview review (hearing review)	**<Understanding proteostasis and discovering innovative medical applications>** **AMED-CREST** **2021 July 29th (tentative)** ***Occasional date: Aug 2nd (tentative)** **PRIME** **2021 July 30th (tentative)** **2021 July 31st (tentative)** ***Occasional date: Aug 2nd (tentative)** **<Understanding of the biological phenomena and responses at the early life stages to improve the quality of health and medical care>** **AMED-CREST** **2021 Aug 6th** **PRIME** **2021 Aug 4th (tentative)** **2021 Aug 5th (tentative)**
Notification of selection/rejection	**Early September 2021 (tentative)**
Date of commencement (contracting, etc.) of R&D Project	**Friday, October 1st, 2021(tentative)**

Note 1. For all proposal's 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. 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 4. Interview reviews (hearing reviews) may sometimes be conducted over the Internet etc.

Note 5. In the case that an interview review (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 an interview review (hearing review) or interview reviews (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 interview reviews (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 cannot answer questions regarding the eligibility of individual projects for interview reviews (hearing reviews).

Note 6. 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 7. As a general rule, the interview review (hearing review) shall be attended by the PI. The date and time of the interview review (hearing review) cannot be changed. Note that interviews will in principle be conducted in Japanese, but that English may be used when conducting the interview in Japanese is impractical.

Note 8. Following the interview review (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 9. The method of interview reviews (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 interview reviews (hearing reviews) are cancelled the period for the document review may be extended.

Note 10. 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 11. 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. AMED will also endeavor to coordinate with the PS/PO, etc. of a project as swiftly as possible to ensure that the contracted R&D agreement can be concluded as early as possible.

Note 12. All time in this table according to Japan Time.

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.

In addition, in order for AMED to contribute to the internationalization of the R&D environment as well as further enhance the quality of project evaluations, it has been decided to include researchers affiliated with an overseas research institution (AMED reviewer) in the ex-ante evaluation process. Accordingly, with regard to the relevant project, at the time of proposal submission, please submit [(Example document name) "Presence/Absence of Items Subject to Export Regulations under the Foreign Exchange and Foreign Trade Act)]. For details regarding security trade control, please refer to Chapter 2.5.3

(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 interview reviews (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 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 the current proposed project.

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.

Document reviews will place particular emphasis on the perspectives stated in (A), (B), and (C), but when necessary the perspectives stated in (D), (E), and (F) will also be taken into consideration. In the interview review (hearing review), evaluations and reviews will be conducted based on all perspectives.

(A) Compatibility with the program's purpose

- Is the project compatible with the program's purpose and objectives, etc.?
  (Does the project contribute to the achievements of the 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?

(D) Implementation system

- Has an R&D system centered on the applicant been organized appropriately?
- Has a sufficient collaboration network been constructed?
  (Does the R&D Co-Investigator play an essential role in realizing the R&D 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?)
- 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. Please note that the forms that must be submitted and the language that should be used will differ depending on the type of research (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 AMED-CREST

No.	Mandatory or optional	Form	Contents	Language
1	Mandatory	Form E1	R&D Proposal Cover Page (in English) 1. Research Objectives 2. R&D Plan and Approaches 3. Research Achievements Annex E1 Main Schedule for R&D	English[1]
2	Mandatory	Form E2	R&D Proposal Cover Page (in Japanese) 4. Status of Research Application, Acceptance, and Effort 5. Past Research Funds/Grants Received and Resulting Achievements Annex E2 Implementation System Diagram Annex E3 R&D Project Organization (R&D PI's Group and Co-Investigator's Group) Annex E4 Ethical Considerations Annex E5 References and Additional Statements	Japanese
3	Mandatory	Appendix E1	Summary or Proposal (in Japanese)	Japanese
4	Mandatory	Appendix E2	Security Trade Control Checklist (in Japanese)[2] Summary of Proposal (in English)	Japanese English
5	Mandatory	Appendix E3	List of project participants (to submit as an Excel format)	English

[1] For the proposed R&D projects in all R&D areas of AMED-CREST, AMED Reviewers affiliated with overseas research institutions will participate in the review process. For this reason, you should fill out and submit Form E1 in English, and also submit Appendix E2 "Security Trade Control Checklist" and Appendix E3 "List of project participants."

[2] The content of Appendix E2 "Security Trade Control Checklist" will not affect the selection results.

All R&D areas for PRIME

No.	Mandatory or optional	Form	Contents	Language
1	Mandatory	Form P1	R&D Proposal Cover Page 1. Research Objectives 2. R&D Plan and Approaches 3. Research Achievements 4. Status of Research Application, Acceptance and Effort 5. Past Research Funds/Grants Received and Resulting Achievements Annex P1 Main Schedule for R&D Annex P2 R&D Project Organization Annex P3 Ethical Considerations Annex P4 References and Additional Statements	Japanese
2	Mandatory	Appendix P1	Summary of Proposal	Japanese
3	Mandatory	Appendix P2	Summary of Proposal	English

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_00003.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.

(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.

5.2 Required Proposal Documents Apart from R&D Proposals

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

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

Note: R&D projects 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.

(2) 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 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)
  http://rinri.med.or.jp/kaisaibi_shinsashinseisho/files/youshiki_rei2.docx (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)

(3) 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.

(4) 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 before the application deadline and

then re-submit the amended documents. For details regarding retrieval procedures, please refer to the Operation Manuals for Researchers. 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: The data file for proposal documents can only be submitted in PDF format. (e-Rad has a feature for converting Word and Ichitaro (Japanese document) files to PDF format. It is not necessary to use this feature for PDF conversion, but if you do use them, be sure to refer to user' manual (Quick Guide for Researchers). If you use foreign-language letters or special characters, the text may be garbled, and so please be sure to check the content of the converted PDF file on the system.)

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

5.3.1 Checking Acceptance Status on the e-Rad

Verifying the acceptance of proposal documents can be done by viewing the "Manage submitted proposals" screen on the e-Rad. 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. 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 the 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 download the research institution registration application form from the e-Rad portal site and then fill out and submit it by postal mail. Registration may require several days, so please allow leeway of two weeks or more for carrying out registration procedures.

Please note that once you have registered 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 register their researcher information and obtain a login ID and password.

The research institution should register information for researchers who are affiliated with it.

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 at the Ministry of Education, Culture, Sports, Science and Technology (MEXT). Please refer to the e-Rad portal site 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

In the case that a researcher is unnecessarily being allocated competitive research funds, etc. from the national government and/or multiple independent administrative agencies (including hereinafter national research and development agencies) for the same R&D project (name or content of the research receiving competitive funds) being

conducted by the same researchers, and if any of the following applies, the R&D project may be eliminated from eligibility for review, the decision to adopt the R&D project may be cancelled, or the amount of funds reduced (hereinafter referred to as "Cancellation of decision to adopt, etc."). Although there are no restrictions on submitting applications for other competitive research funding programs at the stage of applying for this program, please notify the AMED division in charge of this program promptly in the case that your R&D project is adopted by another competitive research funding program. If this is not reported, there is the possibility that the decision to adopt the R&D project under this program will be cancelled.

(A) Applications are submitted simultaneously for multiple competitive research funding programs, etc. 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, etc.

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

(D) Other equivalent cases

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

Accordingly, in the case that a proposal document for an R&D project is submitted to and adopted by another competitive research funding program 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 the decision to adopt the R&D project under this program will be cancelled.

(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* (100%) 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 Provision of Information Related to Application Content in Order to Eliminate Unreasonable Duplication/Excessive Concentration

In order to eliminate unreasonable duplication/excessive concentration, information related to parts of the application content (or awarded project/program content) may be provided within the necessary extent, to the persons in charge of other competitive research funding programs, including other government ministry/agency programs, via e-Rad. Furthermore, in the case that information is requested for checks being conducted under other competitive research funding programs, information may be provided in this way.

5.4.4 Status of Application and/or Acceptance Under Other Competitive Research Funding Programs, Including Other Government Ministry/Agency Programs

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

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 the research institutions to which they are affiliated from being unfairly infringed, the information in question acquired shall be used solely for the work detailed above, and those using it shall be limited to AMED executive officers and staff members involved in the above-mentioned administrative work.

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 its Provisions for Management of Corporate Documents, and in accordance with both the Act on Access to Information Held by Incorporated Administrative Agencies etc. and the Act on the Protection of Personal Information Held by Incorporated Administrative Agency, etc., 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.*

* "Introduction to the information disclosure system in the information disclosure system" section of the website (Ministry of Internal Affairs and Communications)
https://www.soumu.go.jp/main_sosiki/gyoukan/kanri/jyohokokai/shoukai.html (in Japanese)
"Introduction of legal systems in the protection of personal information by government organizations/independent administrative agencies, etc." section of the website (Ministry of Internal Affairs and Communications)
https://www.soumu.go.jp/main_sosiki/gyoukan/kanri/horei_kihon.html (in Japanese)

6.1.2 Necessary Disclosure/Provision of Information

(A) Information related to each adopted project (program title, R&D project title, PI's affiliated institution/position/name, e-Rad project/researcher/research institution number, budget amount, R&D period, 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), and public databases operated by funding agencies, etc., providing cooperation under an agreement, etc., with AMED (World RePORT,[2] etc.)

(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 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. Accordingly, the Council for Science, Technology and Innovation (CSTI) and related government ministries and agencies call for thoroughness in registering accomplishmemt information about academic papers and patents etc., and account records on e-Rad, in order to connect the output/outcome information with the input by solicitation-type research funding programs. For this reason, even after the relevant project has been selected, researchers are requested to input into e-Rad the R&D accomplishment information for each fiscal year (academic papers, patents, etc.) as well as accounting report information and information on actual disbursement of indirect costs related to competitive funding. 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, etc.

[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 Proposal 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

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

(A) Documents required by AMED to be submitted are not submitted by the submission deadline.

(B) A researcher/researcher involved in the relevant R&D project have had their application to/eligibility for participation in AMED R&D programs restricted for a certain period of time.

(C) An investigation has been opened into allegations of misconduct.

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

(E) It is discovered that the R&D project does not fulfill the conditions for application, etc.

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 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 implemented by the national government or independent administrative agencies has ended).[2]

(B) In the case that persons who are the subject of an investigation (hereinafter referred to as the "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 subcontracted institution, including the Co-Investigator or equivalent person affiliated with the subcontracted institution) 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 “subcontracted institution”), 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 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

With regard to awarded projects, the PI is requested to submit* a data management plan (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 the shared 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 storing 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 AMED Guidelines Concerning Utilization of Research Data and the Guide for Completing Data Management Plans. (The AMED Guidelines Concerning Utilization of Research Data 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.
* AMED Guidelines Concerning Utilization of Research Data and obligation of submission of data management plans
https://www.amed.go.jp/koubo/datamanagement.html (in Japanese)

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 one-fiscal-year contracted R&D agreement shall be concluded between the research institution implementing the R&D project and AMED in accordance with the principle of the accounting period of the national government. Successful applicants shall receive detailed information from AMED following project selection.

In concluding contracted R&D agreements, in the case that 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., and agreement is not reached regarding both the content of the agreement (including expenditure estimates) and method, an agreement may not be concluded even for an awarded R&D project.

Even after the contracted R&D agreement has been concluded, in the case that unavoidable circumstances arise due to budget restrictions, the R&D 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 subcontracted institution and the subcontracted institution 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 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 Integrated Innovation Strategy 2019 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). (However, the ceiling for buyout expenses shall be 2 million yen under PRIME projects.)

	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 (including personnel costs for PIs and Co-Investigators[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 results publication costs (academic paper contribution costs, academic paper offprint costs, website production costs, etc.), conference costs, equipment leasing costs, Equipment repair costs, printing costs, subcontract costs, licensing fee, expenses for entrusting other persons with PIs' work other than research and development ordinarily performed by PIs at their affiliated institutions (buyout expenses), [2] 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, 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, special private 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 details, please refer to the AMED website below.[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 order to mitigate the expenses involved in the use of computers and aim for effective cost management to accelerate research, AMED provides all R&D projects with a joint service for using the Tohoku University Tohoku Medical Megabank Organization's supercomputer at a special rate. Those planning to use this service should calculate the costs by referring to the Tohoku University Tohoku Medical Megabank Organization Supercomputer Usage Fee Rules.[3]

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

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

[3] https://sc.megabank.tohoku.ac.jp/wp-content/uploads/2019/04/uses_fee_20190401.pdf (in Japanese)

8.2.3 Encouragement of Shared Use of Research Equipment

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

* 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 fund" (revised on July 18, 2019 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 and Research Institutions,[1] through direct costs (hereinafter referred to as "Acquired Goods") shall revert to the university, etc.[2]

Ownership of acquired goods by Companies, etc.,[3] 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 and Research Institutions" 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-service corporations, that are recognized by AMED

[2] The submission of contracted research regulations etc. will be necessary in the event that goods acquired using contracting expenses are made the property of a university.

[3] "Companies, etc." is a general term for research institutions other than "Universities and Research Institutions."

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 overall program budget conditions, R&D Area management actions taken by the PS and PO, or factors such as the results of R&D evaluations.

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 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 five years or longer shall undergo a Mid-term Review by the Project Evaluation Panel at around the third year after the R&D commences to rigorously evaluate the degree to which the R&D plan is being achieved and R&D accomplishments, etc.* Awarded projects whose planned R&D period is less than five years are not required to undergo a Mid-term Review as a general rule, but in the case that it becomes necessary to conduct a Mid-term Review in the course of implementing the program, a Mid-term Review shall be conducted by the Project Evaluation Panel. Furthermore, in the case that it is deemed necessary, 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.

*"Five years" refers to five fiscal years.

9.3 Presentations at Accomplishments Report Meeting

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

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 R&D Accomplishments Reports

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. 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.

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 results 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, 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 of FY2020 onwards and the AMED Guidelines Concerning Utilization of Research Data.*

* 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 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 Research Ethics Education Program

As part of measures to prevent misconduct from occurring, AMED requires all researchers participating in this program to take and complete a research ethics education program. Accordingly, research institutions shall implement research ethics 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 research ethics education program, execution of contracted R&D funds may be suspended until completion of the research ethics education program is confirmed.

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

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

• 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 (in Japanese)

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 training 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 Research Ethics Training Period

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

11.3.3 Role of Research Institutions and Reporting Research Ethics Training Status

Research institutions shall ensure that persons required to undergo research ethics training as listed above who are affiliated with their institution (included a subcontracted institution) undergo the R&D ethics education using one of the programs/materials listed above; compile information on researchers' R&D ethics education status; and submit a report on the status of training on the form prescribed by AMED by e-mail to AMED (Division of Research Integrity and Legal Affairs, Department of Research Integrity and Project Management). (Seal need not be affixed.).

Information regarding where and how to submit reports is to be posted on the "The Responsible Conduct of Research (RCR) Education Program" page under "Research Integrity" on the AMED website (refer to URL shown above) around March 2021.

• Subject of report	Persons required to undergo research ethics training in programs commencing in/after FY2021
• Deadline for submission	May 31, 2022
• Documents to be submitted	Report on the Status of Participation in R&D Ethics Education Programs (Please download the form from the AMED website)
• URL	https://www.amed.go.jp/kenkyu_kousei/kyoiku_program.html (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 AMED website.*

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* around March 2021.

* 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. 106 of 2006)
- ○ 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)
- ○ 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 March 27, 1997)
- Ministerial Ordinance on Good Clinical Practice for Medical Devices (Ordinance of the Ministry of Health, Labour and Welfare (MHLW) No. 36 of 2005)
- Ministerial Ordinance on Good Clinical Practice for Regenerative Medical Products (Ordinance of the Ministry of Health, Labour and Welfare (MHLW) No. 89 of 2014)
- Ministerial Ordinance on Good Laboratory Practice for Nonclinical Safety Studies of Drugs (Ordinance of the Ministry of Health, Labour and Welfare (MHLW) No.21 of 1997)
- Ministerial Ordinance on Good Laboratory Practice for Nonclinical Safety Studies of Medical Devices (Ordinance of the Ministry of Health, Labour and Welfare (MHLW) No.37 of 2005)
- Ministerial Ordinance on Good Laboratory Practice for Nonclinical Safety Studies of Regenerative Medical Products (Ordinance of the Ministry of Health, Labour and Welfare (MHLW) No.88 of 2014)

- Guidelines on the Handling of Specified Embryos (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) No. 31 of 2019)
- 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)
- 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)
- 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)
- Guidelines on the Research on Producing Germ Cells from Human iPS Cells or Human Tissue Stem Cells (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) No. 88 of 2010)
- Ethical Guidelines for 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 February 28, 2017)
- On the Approach of Research and Development Using Human Tissues Obtained from Surgery (Report of the Health Science Council, the Ministry of Health and Welfare, 1998)
- Ethical Guidelines for Medical and Health Research Involving Human Subjects (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology (MEXT), and Ministry of Health, Labour and Welfare (MHLW) No. 1 of 2017; partially revised on February 28, 2017)
- Ethical Guidelines for Human Genome/Gene Analysis Research (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology (MEXT), the Ministry of Health, Labour and Welfare (MHLW) and the Ministry of Economy, Trade and Industry (METI) No. 1 of 2013; partially revised on February 28, 2017)
- 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 February 28, 2019)

○ Fundamental Guidelines for Proper Conduct of Animal Experiments and Related Activities in Academic Research Institutions (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) No. 71 of 2006); Fundamental Guidelines for Proper Conduct of Animal Experiments and Related Activities in Implementing Agencies under the Ministry of Health, Labour and Welfare (Notification by Director, Health Science Division, Minister's Secretariat, Ministry of Health, Labour and Welfare (MHLW) on June 1, 2006; partially revised on February 20, 2015); and Fundamental Guidelines for Proper Conduct of Animal Experiments and Related Activities in Implementing Agencies under the Ministry of Agriculture, Forestry and Fisheries (Notification by the Director-General of the Secretariat, Agriculture, Forestry and Fisheries Research Council, Ministry of Agriculture, Forestry and Fisheries (MAFF) on June 1, 2006)

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

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

- MEXT's Life Sciences Forum "Initiative on Bioethics and Biosafety"
  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 18, 2014).

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

- Guidelines for Responding to Misconduct in Research
  https://www.mext.go.jp/b_menu/houdou/26/08/1351568.htm
- Guidelines for Management and Audit of Public Research Funds at Research Institutions (implementation standards)
  https://www.mext.go.jp/a_menu/kansa/houkoku/1343904.htm (in Japanese)

11.6.2 Confirmation of System Maintenance

[In concluding the agreement for /In applying 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.

According to the format of the various websites all research institutions are requested to submit a checklist to MEXT via e-Rad by the deadline stipulated separately by AMED on or after April 1, 2021.

(A) Self-evaluation (Including System Maintenance) Checklist	
• Basis	Guidelines for Management and Audit of Public Research Funds at Research Institutions (implementation standards)
• Submission method	https://www.mext.go.jp/a_menu/kansa/houkoku/1301688.htm (in Japanese)
• Submit to	Office of Research Funding Administration, Policy Division, Research Promotion Bureau, MEXT
(B) Checklist of research misconduct	
• Basis	Guidelines for Responding to Misconduct in Research
• Submission method	https://www.mext.go.jp/a_menu/jinzai/fusei/1374697.htm (in Japanese)
• Submit to	Office for Research Integrity Promotion, Human Resources Policy Division, Science and Technology Policy Bureau, 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 this fiscal year when applying for a MEXT program, it is not necessary to newly submit a checklist when applying for another MEXT program or concluding a contracted R&D agreement in the same fiscal year.

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 funding of MEXT or independent administrative agencies under MEXT are not required to submit the checklist, likewise, with regard to the checklist (B) above institutions that do not conduct research activities and institutions that conduct research activities but are not allocated a budget by the independent administrative agencies under MEXT are not required to submit the checklist.

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

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

Note that in this case, AMED may order the accused and/or the research institution to suspend use of research funds under this program as a temporary measure during the 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); Guidelines for Management and Audit of Public Research Funds at Research Institutions (implementation standards) (decided by the Minister of Education, Culture, Sports, Science and Technology on February 15, 2007; revised on February 18, 2014); and AMED Regulations for Responding to Misconduct in Research Activities.

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

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, research project, budget amount, fiscal year of research, details of the misconduct and details of measures taken against them etc.). In this way competitive 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 Misconduct	1. Especially malicious individual who intentionally engages in misconduct from the outset of the research		10 years

<table>
<tr><td rowspan="4"></td><td rowspan="3">2. Author of academic paper, etc. related to research in which there has been misconduct</td><td rowspan="2">The author responsible for the academic paper in question (supervisor, first author, or other position of responsibility deemed equivalent)</td><td>The impact on the advancement of research in the relevant field or society is large, and the maliciousness of the misconduct is deemed to be high.</td><td>5–7 years</td></tr>
<tr><td>The impact on the advancement of research in the relevant field or society is small, and the maliciousness of the misconduct is deemed to be low.</td><td>3–5 years</td></tr>
<tr><td>Author other than that listed above</td><td></td><td>2–3 years</td></tr>
<tr><td colspan="2">3. An individual involved in misconduct other than that stipulated in 1 or 2</td><td></td><td>2–3 years</td></tr>
<tr><td colspan="3" rowspan="2">An author responsible for academic papers, etc. related to research in which there has been misconduct but who was not involved in the misconduct (supervisor, first author, or other position of responsibility deemed equivalent)</td><td>The impact on the advancement of research in the relevant field or society is large, and the maliciousness of the misconduct is deemed to be high.</td><td>2–3 years</td></tr>
<tr><td>The impact on the advancement of research in the relevant field or society is small, and the maliciousness of the misconduct is deemed to be low.</td><td>1–2 years</td></tr>
</table>

• In the case of fraudulent use/fraudulent receipt

The period of restriction deemed appropriate in consideration of the content 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.

Researchers involved in fraudulent use or receipt	Severity of fraudulent use	Period of application restriction

<table>
<tr><td>whose applications will be restricted</td><td colspan="2"></td><td></td></tr>
<tr><td rowspan="4">1. Researcher who perpetrated fraudulent use and conspiring researchers</td><td colspan="2">(1) Personal diversion of funds for private benefit</td><td>10 years</td></tr>
<tr><td rowspan="3">(2) Other than (1)</td><td>i) The researcher’s actions are deemed to have a large social impact and be highly malicious.</td><td>5 years</td></tr>
<tr><td>ii) Those other than i) and iii)</td><td>2—4 years</td></tr>
<tr><td>iii) The researcher’s actions are deemed to have a small social impact and be slightly malicious.</td><td>1 year</td></tr>
<tr><td>2. Researchers who received competitive funds through falsehoods or other dishonest means and conspiring researchers</td><td colspan="2"></td><td>5 years</td></tr>
<tr><td>3. Researchers not directly involved in fraudulent use but who use the research funds in a manner infringing duty of diligence</td><td colspan="2"></td><td>Maximum of two years and minimum of one year depending on the severity of infringement of diligence by the researcher with duty of diligence</td></tr>
</table>

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

- In 1, the researcher’s actions are deemed to have a small social impact and be slightly malicious, and the funding amount used fraudulently is small.
- In 3, the researcher’s actions are deemed to have a small social impact and be slightly malicious.

Note 2: With regard to 3 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 Funding Programs etc. Has Been Restricted

With regard to researchers who have been found to have carried out misconduct under competitive funding programs etc. (including programs for which new applications are solicited in FY2021 or later, and programs completed in or before FY2020) 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 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 Funding Program

In the case that there is a complaint, etc., that a researcher participating in this program is suspected of perpetrating misconduct under another competitive funding program, the research institution with which the relevant researcher is affiliated is obligated to report to AMED that an investigation of the relevant misconduct allegations has been implemented. Please note that, on receipt of this report, AMED may order the temporary suspension of usage of contracted R&D funds if deemed necessary.

Furthermore, in the case that the research 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); Guidelines for Management and Audit of Public Research Funds at Research Institutions (implementation standards) (decided by the Minister of Education, Culture, Sports, Science and Technology on February 15, 2007; revised on February 18, 2014); and AMED Regulations for Responding to Misconduct in Research Activities. In 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 R&D ethics education and the officers in charge of promoting compliance (collectively referred to as “Research Integrity Officers” or RIO) who are participating in AMED programs should become members of the RIO Network.

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

* 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 Dialogue and Cooperation with Citizens and Society

According to "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), if a proposal is selected in this call for proposals and receives an allocation of public research funds (competitive funds or project research funds) in an amount of 30 million yen per year or more for one project, it is considered essential to have an attitude in which excellent achievements in science and technology are constantly produced, and achievements in science and technology are returned to the public in order to further develop science and technology in Japan, and science and technology are advanced jointly with the understanding and support of the public through "Dialogue on Science and Technology with the Public." In addition, the 5th Science and Technology Basic Plan (Cabinet decision of January 22, 2016) calls for deepening the conventional relationship, in which science and technology and society are opposed, into a relationship of dialogue and cooperation by various stakeholders, i.e., researchers, citizens, the media, industry, and policymakers, in other words, a relationship that promotes "co-creation." From these viewpoints, efforts to explain the content and results of research activities to society and the public in easily understood terms, and efforts to promote dialogue and cooperation among various stakeholders are demanded. Based on this, we ask that program participants make active efforts in connection with these activities, including holding public lectures and symposiums on research achievements, continuously posting information on research achievements 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)

Reference: Fifth Science and Technology Basic Plan
https://www8.cao.go.jp/cstp/kihonkeikaku/5honbun.pdf (in Japanese)

13.2 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 results in the medical field as quickly as possible and delivering these results to patients and their families. In view of this mission, AMED is promoting initiatives that promote Patient and Public Involvement (PPI)* in medical research and clinical studies. These efforts are expected to generate research results that are even more beneficial to patients, etc., as well as lead

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

* AMED's definition of "Patient and Public Involvement (PPI) in Medical Research/Clinical Studies"

As part of the medical research/clinical study process, researchers are endeavoring to incorporate the knowledge and opinions of patients and members of the general public. Here, "Patient and Public" includes patients, patients' families, former patients (survivors), and future patients.

Reference: AMED's "Patient/Public Involvement (PPI) in Medical Research/Clinical Studies"

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

13.3 Health Risk Information

In accordance with requests from the Ministry of Health, Labour and Welfare, AMED requires researchers to report information obtained in the process of conducting research that could seriously threaten the lives and/health of members of the general public (hereinafter referred to as "Health risk Information") to the Ministry of Health, Labour and Welfare using the prescribed form.[1] For details such as contact information, please refer to the AMED Administration Manual for Contracted R&D Agreement in Japan Agency for Medical Research and Development.[2]

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

[1] 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)

13.4 Smoothing Utilization of Research Tool Patents

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

13.5 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

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

13.6 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 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[1] provides 1) IP strategy advice aimed at appropriate out-licensing at the early stages of R&D, 2) investigations of the available literature, markets research and support for technical seeds evaluation, and 3) guidance for the creation of appropriate PR sheets on R&D accomplishments for exhibitions and business negotiations.

If you wish to receive the support mentioned above, please contact AMED's Medical IP Desk (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)

13.7 Seeds/Needs Matching Support System

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 results in the medical field. This enables research seeds to be showcased to staff in charge of in-licensing at multiple 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)

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

In order to link the results of outstanding basic research by universities to the practical application of drugs, AMED's Department of Innovative Drug Discovery and Development (hereinafter referred to as the "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 on the premise of maintaining confidentiality and protecting IP rights that have reverted to the researcher.

In the same way, with regards to the applied R&D projects related to drug development that is or was supported by the 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.

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

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

13.10 Registration of Researcher Information on researchmap

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

Note that there is a link from researcher names on the AMED funding for innovation database (AMEDfind) website to researchmap.

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

13.11 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[2] the relevant bioresources in domestic resource centers,[1] and make them broadly available for researchers' use.

[1] 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 and so on.

[2] "Deposit": Procedure for permitting the use (storage/provision) of resources at domestic resource centers etc. listed in 1 above 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.

13.12 Cooperation with Databases

(1) Publicizing of Data from the National Bioscience Database Center

The National Bioscience Database Center (NBDC) (https://biosciencedbc.jp/en/) was established in April 2011 in the Japan Science and Technology Agency in order to promote the integrated use of the life science database that has been created through the efforts of many 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 Center playing a central role.

Based on this, you are asked to cooperate with the provision of data to the Center with regard to the following types of data and databases resulting from this program.

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	Copies of data concerning results published in academic papers, or other means, or copies of 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, Labour 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.

13.13 Reform of Competitive Research Founding

Currently, improvements regarding the systems for competitive research funds are being promoted, with the Integrated Innovation Strategy 2019 and the Comprehensive Package for Research Competitiveness Enhancement and Young Researcher Support.

Based on this, improve system for competitive research founds has been discussed to enable more effective and efficient managements for research founds.

In this way, we will inform you when a common policy to every competitive research founds indicates and it will be applied to this programs.

13.14 Improvement of Incentives for Doctoral Students

The Fifth Science and Technology Basic Plan of the Japanese government, in an attempt to lure outstanding students and experienced professionals form within and outside Japan, states as one of their numerical targets to implement financial aid for doctoral students attending the latter part of the course (hereinafter referred to as "doctoral students"): "We will strive to enable 20 percent of doctoral students to receive an amount equivalent to their living expenses." Accordingly, there is a need to expand the employment and improve the treatment of doctoral students as research assistants (RAs) in universities and research and development agencies. Moreover, the Comprehensive Package to Strengthen Research Capacity and Support Young Researchers (formulated on January 23, 2020, by the Council for Science, Technology and Innovation) sets the objective of "enabling in the future doctoral students who so wish to be paid amounts commensurate with their living costs," and as a specific measure cites "promoting the securement of an appropriate salary level for RAs and so on paid from competitive research funds and joint research funds."

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 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. 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

- Salary level (approx. 1.8 million to 2.4 million per year) equivalent to living expenses*

  With reference to the fact that the annual sum of 1.8 million yen is envisaged as being commensurate with living expenses in the Fifth Science and Technology Basic Plan, and the amount of the grants-in-aid for the JSPS Research Fellows (DC) that allows outstanding doctoral students to dedicated themselves to their research without financial anxiety, the rule of thumb for the scope of the sum required for living expenses is between 1.8 million and 2.4 million yen.

- 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. The salary level indicated above does not restrict salary payments of either a higher or lower amounts.
- 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.

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

Since both "Improving and Reforming Research Capability 2019" (formulated on April 23, 2019 by MEXT) and "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) points out that with regard to fixed-term positions such as specially appointed faculty members and postdoctoral fellows short-term appointments may hinder their career development, and securing tenures of five years or more is important.

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 of the R&D period, having checked with the persons in charge of personnel and accounts in the relevant department, and also make an effort to, as far as possible, secure tenures of five years or more through the utilization of other external funding such as indirect expenses, basic expenses and donations.

13.16 Support for Diverse Career Paths for Young Researchers

According to the "Basic Policy on Support for Diverse Career Paths for Young Postdoctoral Fellows to Be Employed through MEXT Public Research Funds" (formulated on December 20, 2011 by MEXT's Council for Science and Technology's Personnel Committee), "The public research institutions and their representatives should eagerly involve themselves in the support of young postdoctoral researchers in order to secure for these young people a variety of career paths inside and outside of Japan." In response to this statement, those involved in the projects adopted 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 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 Accreditation of Partnership on Research Assistance Service (A-PRAS)

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 results 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. It aims through 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, to improve researchers' research environments, promote science and technology in Japan, accelerate the creation of innovation, and support the development of a variety of initiatives regarding research assistance services.

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 and Legal Affairs, Department of Research Integrity and Project Management, AMED E-mail: kouseisoudan "AT"amed.go.jp
Management of conflict of interest/research ethics education programs	Division of Research Integrity and Legal Affairs, Department of Research Integrity and Project Management, AMED E-mail: kenkyuukousei"AT"amed.go.jp
RIO Network	Division of Research Integrity 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: 0570-066-877 (NAVI-DIAL) or +81-3-6631-0622 (direct line) if the NAVI-DIAL service is unavailable. Operating hours: 9:00–18:00 (weekdays) *Excludes Saturdays, Sundays, public holidays, or Year-end/New Year holidays (December 29 – January 3)
Bioscience Database	Japan Science and Technology Agency (JST) National Bioscience Database Center (NBDC) Tel: 03-5214-8491 E-mail: nbdc-kikaku"AT"jst.go.jp

Chapter 15. (Reference) Research and Development Objectives

15.1 Research and Development Objective: Understanding and medical application of proteostasis

1. Objective Title

Understanding and medical application of proteostasis

2. Overview

With the recent development of genome analysis technology, the relationship between various diseases and gene mutations has become clear, but there are still many diseases of which the molecular mechanism leading to the onset is unknown. Many cohort studies have found cases in which disease-related genes do not necessarily cause disease. In future disease studies, it is necessary to deepen the understanding of the process of post-translational modification (glycosylation, oxidation, glycation, etc.) and control of translation, in addition to analysis of expression of gene and protein. However, research on proteins, which are structurally diverse and alter their structure and function with post-translational modifications in response to the surrounding environment, has lagged behind research on nucleic acids, which have relatively simple structures and are easy to handle.

This research and development objective aims to clarify the structural and functional relationships of proteins through biochemical and structural biological approaches to protein homeostasis (proteostasis*), denaturation, aggregation, and degradation of proteins that cause an irreversible reaction, and post-translational modifications that have an irreversible effect on protein function, in order to create seeds that will contribute to the future health maintenance, by clarifying the molecular mechanism leading to various diseases. In addition, basic and clinical researchers in the fields of structural biology, immunology, metabolism, and the nervous system, as well as researchers from different fields such as analytical chemistry and bioinformatics, will gather together in addition to the protein and sugar chain research fields to promote innovative and highly unique research and development by utilizing the strengths of each other's fields.

*"proteostasis" means a series of processes that control the amount, quality, and localization of proteins in the homeostatic maintenance function of living organisms.

3. Goals and Objectives

Focusing on the homeostasis of proteins inside and outside the cell (proteostasis), this research and development objective aims to clarify the mechanism of disease onset and create innovative medical technologies by analyzing the dynamics of degeneration, aggregation, decomposition, etc. from the cell to the individual level. In particular, the following four targets are to be achieved:

(1) Improved understanding of the environment surrounding proteins involved in proteostasis at the molecular level

(2) Elucidation of the mechanism of diseases onset resulting from disruption of proteostasis

(3) Development of seeds for therapeutic drugs and biomarkers targeting the mechanisms by which proteostasis disrupts

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 in the following ways:

- Early discovery and treatment of degenerative diseases, which are becoming a global problem as populations age, and diseases for which there are currently no effective treatment methods
- Even longer healthy life expectancies as daily lifestyle habits are improved in light of biochemical evidence

5. Specific Research Examples

(1) Improved understanding of the environment surrounding proteins involved in proteostasis at the molecular level

The research will use structural and functional analytical methods to elucidate the mechanisms controlling protein denaturation, degradation, and aggregation, as well as homeostatic mechanisms as proteins fluctuate inside and outside the cells. Below we provide specific examples of the anticipated research.

- Understand physical and biochemical signals within the cell that control protein denaturation, degradation, and aggregation.
- Evaluate nuclear protein fluctuations that are involved with chromatin regulation and gene expression within the nucleus.
- Understand the mechanisms behind 3D structures involving protein denaturation/aggregation and folding and expression of cell toxicity.
- Understand the mechanisms by which modifying glycans control proteostasis.
- Conduct 3D structural analysis of glycoproteins and glycans using technologies that can visualize structures at a high resolution.
- Understand the early-stage processes occurring in vivo inside and outside the cells, including protein denaturation and aggregation, and the molecular mechanisms of the processes involved in progression (including environmental factors, location information, and posttranslational modifications); also understand control mechanisms in vivo (e.g., disaggregation and degradation).
- Understand the environmental factors, biochemical structural changes, and molecular pathways involved in glycation, oxidation, and other non-enzymatic modifications, and analyze functional changes in modified proteins.
- Analyze the correlation between structure and function and how special glycosylation molecules, other than N-glycans and mucin glycans, affect protein function; detailed analysis of the glycoproteome.

(2) Elucidation of the mechanism of diseases onset resulting from disruption of proteostasis

This research will use high quality animal models and human disease samples to analyze how failure of protein homeostasis that leads to abnormal modifications and denaturation/aggregation is related to disease. Below we provide specific examples of the anticipated research.

- Identify the mechanisms involved in the recognition and response to denatured/aggregated proteins (abnormal proteins) and abnormal modifications in vivo or molecule species that exhibit cytotoxicity, and

understand the mechanisms of disease onset, such as analysis of the molecular mechanisms that manifest as toxicity.

- For proteins in cell surface receptors and adhesion molecules, understand control mechanisms regulating protein physiological functions that involve various glycoconjugates in the cell-surface environment or changes in site-specific glycosylation, and understand the mechanisms of disease onset mediated by modified proteins.
- Understand the mechanisms behind abnormal protein synthesis based on abnormalities in the protein translation mechanism and understand the molecular mechanisms involved when these abnormal proteins affect cells and tissues in the body.
- In extracellular matrix domains in disease tissues, understand the molecular mechanisms involved in the processes of protein denaturation and aggregation caused by various environmental factors and biologic factors and understand the mechanisms leading to changes in tissue function
- In human disease tissues, conduct biochemical and structural biological analyses of post translation modifications and abnormal proteins, taking into account location information, and develop widely-applicable experimental models based on these findings.
- Create mathematical models using bioinformatics methodologies that can model and predict the molecular mechanisms leading to disease onset, in light of biochemical and molecular biological evidence on protein denaturation/aggregation and posttranslational modifications.

(3) Development of seeds for therapeutic drugs and biomarkers targeting the mechanisms by which proteostasis disrupts

Conduct research that can lead to the development of potential biomarkers and therapeutic agents that target the mechanisms involved in protein denaturation, aggregation, and degradation when protein homeostasis fails. Below we provide specific examples of the anticipated research.

- Use proteostasis as the basis for the development of diagnostic and therapeutic methods against intractable and undiagnosed diseases.
- Create technologies to control (e.g., suppress toxicity, promote degradation) the synthesis and spread of abnormal proteins.
- Develop therapeutic methods using cell engineering and chemical technologies that enable control of site-specific glycan structures and control of the nonuniformity of glycosylation.

6. Domestic and International Research Trends

The technological revolution in recent years has led to the emergence of technologies like next-generation sequencers (and use of this technology for ribosome profiling methods), mass spectrometry, cryo-electron microscopes, and solid-state NMR, which in turn has resulted in the accumulation of new findings and radical changes in the world of proteome research. There have also been rapid advances in analytical and synthesis technologies. Over the past few years, these technologies have proved extremely useful in protein research applications.

Domestic trends

Japan has conducted research into protein physiological functions and protein aggregation, denaturation, modification, and degradation in recent years, through the Japan Science and Technology Agency's Exploratory Research for Advanced Technology (JST-ERATO) program's Mizushima intracellular degradation project (FY2017–22), as well as a number of projects under the Grant-in-Aid for Scientific Research (Kakenhi) on Innovative Areas program including Target recognition and expression mechanism of intrinsically disordered protein (FY2009–13), New aspect of the ubiquitin system: its enormous roles in protein regulation (FY2012–16), Multidisciplinary research on autophagy: from molecular mechanisms to disease states (FY2013–2017), New frontier for ubiquitin biology driven by chemo-technologies (FY2018–22), Multimode autophagy: Diverse pathways and selectivity (FY2019–23), and Nascent-chain biology (FY2014–18). Within the field of protein research, Japan has particular strengths in such areas as organelle stress and ubiquitin, as well as in autophagy, for which a Japanese scientist was awarded the Nobel Prize. In recent years, other Japanese researchers have discovered completely new basic principles that have overturned the conventional wisdom thus far, relating to various early-stage proteins and glycans, including research into glycosylation in organelles and protein folding plus protein quality control.

Areas of glycan research where Japan has particular expertise include world-class contributions to the purification of enzymes that synthesize glycans, the identification and cloning of glycogenes that synthesize glycans, research into glycan biomarkers in cancer, and the development of imaging technologies using glycans. Progress is also being made in up-and-coming research into how proteins and glycans interact. Japan has a history of taking the lead role in glycan research worldwide and Japanese researchers have taken the initiative in various joint symposia with overseas colleagues. International academic societies have also awarded a number of Japanese researchers with international prizes.

International trends

A wealth of research is underway worldwide, such that international conferences on protein research have now become annual events.

Japan, the US, and Germany have started an international consortium on protein research, with proteostasis as one of the core themes. A meeting is planned in Germany in 2020.

In terms of international trends in glycoscience, the Human Proteome Organization (HUPO), an international protein research body founded in 2001, is running the Human Glycoproteomics Initiative as one of its international research projects (HUPO Initiatives), in order to promote research and international collaboration on glycoproteins, driven in particular by Japanese researchers. International meetings have been held thus far all around the world, including in the US, Germany, Netherlands, France, China, Korea, and Taiwan. In 2018, GlySpace was initiated by Japan, the US, and Europe as a scientific community for sharing trustable information on glycans.

7. History of the investigations

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. As a result of further analysis with reference to the above questionnaire-based survey results and expert briefings, protein synthesis through to denaturation and degradation was highlighted as a key area. Then, "Innovative medical discoveries based on protein lifespan" was designated as the key research trend, with the goals of accumulating findings on 1) denaturation, aggregation, and degradation reactions that determine an irreversible path for proteins and 2) glycosylation and other posttranslational modifications that affect protein function, and developing an understanding of the importance of these findings in medical applications.
3. In November 2019, MEXT and AMED co-hosted a workshop to bring together industry and academic experts in the key research trend of "Innovative medical discoveries based on protein lifespan". Delegates at the workshop discussed noteworthy trends in Japan and overseas, the direction of research and clinical applications, and the objectives that should be achieved during research programs. This R&D objective was then created to reflect the workshop discussions and expert briefings.

8. Relevant descriptions included in Japanese Cabinet documents

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

Chapter 3 (1) <2> i)

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

The Healthcare Policy (Cabinet decision dated 22 July 2014, partially revised on 17 February 2017)

Chapter 2. (1) 1)

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

Growth Strategy 2017 (Cabinet decision dated 9 June 2017)

Chapter 2 I. 1. (2) iii)

The government will also advance the research and development of biomarkers and risk markers that allow symptoms of lifestyle diseases and dementia to be detected, at the same time verifying the usefulness of the biomarkers

developed. The government will also advance the research and development of pharmaceuticals and other items that are expected to be utilized for the prevention of lifestyle diseases and dementia.

9. Miscellaneous

In terms of programs relevant to this R&D objective, the Japanese Strategic Objective FY2020 “Intracellular network dynamics and functions” will promote the discovery of analytical technology platforms aimed at understanding dynamic structures, locations, and amounts of intracellular higher-order assemblies and the causality with function. We look for research to progress in an efficient and effective manner, including technology-related activities linked to this R&D objective.

We also look for research to progress in an efficient and effective manner through the linking of this R&D objective with progress in other protein research, namely the JST-ERATO program’s Mizushima intracellular degradation project (FY2017–22) and the projects, under the Grant-in-Aid for Scientific Research (Kakenhi) on Innovative Areas program, of New frontier for ubiquitin biology driven by chemo-technologies (FY2018–22) and Multimode autophagy: Diverse pathways and selectivity (FY2019–23).

In addition, we hope for the formation of international networks as needed in order to reflect overseas research trends including multinational research projects.

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

1. Objective Title

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

2. Overview

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

There have been astonishing progresses in recent years in the development of more sophisticated omics and imaging technologies, and in various research fields including developmental biology, metabolism, immunology, and neuroscience. Researchers in Japan and overseas have started to systematically gather basic information from various model animals or data/samples from human birth cohorts and are developing platforms for integrated research aimed at understanding of the biological phenomena at the molecular level during early life stages, the mechanisms involved,

and the impact of environmental factors from the early stages of life through to the next generation. As such, this R&D objective is aimed at more comprehensive understanding of the impact on the body from environmental factors at the early stages of life by combining diverse approaches of biology and medical science, agriculture, engineering, and informatics. In the future, we hope that this research will provide evidence to underpin the development of more sophisticated preventive interventions and therapeutic technologies and to contribute to better quality health and medical care (including maternal and child health).

3. Goals and Objectives

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

(1) Understanding: Improve our understanding of the biological phenomena and responses at the early stages of life and clarify the molecular mechanisms involved

(2) Technology: Establish platform technologies to enable high-precision measurements that can be applied to the studies on the early stages of life and develop their applications

(3) Control: Identify key response factors at the early stages of life and generate seeds for preventive, diagnostic, and therapeutic technologies

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

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

- We can become a healthy and sustainable society if we can overcome a range of issues relating to maternal and child health and the birth of the next generation (including infertility or low birth weights).
- Our society can achieve a revolution in healthcare if we can take a preemptive-healthcare approach against various diseases (including developmental disorders, lifestyle-related disease, and allergies) where effective interventions can be made in the early stages of life and overcome diseases even after onset.
- We can become a society where there are accelerating improvements in lifestyle habits and the environment due to the dissemination of evidence-based guidelines etc., and where various diseases can be prevented, healthy lifespans can be extended, and the social security burden can be reduced.
- Our industries can become more competitive if we apply the seeds generated through this research to the further development of the health industry (such as nutritional foods) and drug development.

5. Specific Research Examples

(1) Understanding: Improve our understanding of the biological phenomena and responses at the early stages of life and clarify the molecular mechanisms involved

- Understand the mechanisms underlying biological responses to environmental factors at the early stages of life (from fertilization to young adult) in both animal models and humans (including clarification of the corresponding basis for physiological homeostasis), by combined approaches of developmental

biology, metabolism studies, immunology, and neuroscience.

- Clarify the mechanisms by which biological responses at the early stages of life have an impact on wellbeing and disease at the middle-to-late stages of life and how the health of subsequent generations is affected

(2) Technology: Establish platform technologies to enable high-precision measurements that can be applied during the early stages of life and develop their applications

- Develop analytical systems using animal models or human stem cells/organoids, long-term imaging technologies, or single-cell omics, and applications for cohort samples etc.
- Develop applications for integrative analysis of multi-omics data and imaging, higher-level mathematical modelling, or disease prognoses

(3) Control: Identify key response factors at the early stages of life and generate seeds for preventive, diagnostic, and therapeutic technologies

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

6. Domestic and International Research Trends

Domestic trends

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

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

International trends

More and more papers are being published on the results of birth cohort research over the past 50 years or more in the UK, Holland, and elsewhere, with the results supporting a relationship between the environment in the early stages of life and development/growth, as well as with subsequent disease in the life stages from adulthood into old age. The rapid developments in epigenomic and metabolomic analytical technologies in the 2010s have resulted in epidemiological findings as well as a better understanding of the mechanisms involved at a molecular level. As a result, various R&D programs in Europe and the US, for example at the National Institutes of Health (NIH) in the US, have been initiated to better understand and attempt to control various phenomena at the early stages of life (including metabolism, nutrition, immunity, microbiomes, reproduction, and ontogeny).

7. History of the investigations

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

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

8. Relevant descriptions included in Japanese Cabinet documents

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

Introduction

… the translation of Japan's basic scientific research into efforts to promote the development of the world's most advanced medical technology and the extension of healthy life expectancy through medical care that utilizes the results

of these efforts is a pressing issue, as is the need to ensure the sustainability of Japan's health care system. Moreover, it would be fair to say that medical care initiatives focused on the children who will support our society in the future are currently inadequate.

I-1-(1)-(b)

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

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

2-2-2

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

9. Miscellaneous

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

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