BBJ Sample and Data Utilization Guidelines

Established on September 14, 2018
Revised on April 1, 2019
Revised on December 23, 2020

Contents

I Introduction

Under the "Tailor-made Medical Treatment Program (1st and 2nd)," which was started as a program entrusted by the Ministry of Education, Culture, Sports, Science and Technology in fiscal 2003, and a new phase of the "Tailor-made Medical Treatment Program," the Institute of Medical Science, The University of Tokyo, which served as the central body of the program, established "BioBank Japan (BBJ)" within its organization and installed storage facilities with fully automatic conveying systems, one of which can store about 2,000,000 tubes at 4°C and another of which can store about 480,000 tubes at -150°C, and a manual-type storage facility that can store about 3,300,000 at -150°C. With the cooperation of 12 domestic medical institutions and Riken, BBJ collected clinical information and biological samples (DNA and serum) for 51 diseases of about 266,000 patients (about 420,000 cases) and conducted genomic analyses utilizing these samples. BBJ stored and managed the samples and information and provided them to domestic researchers.

In April 2018, the former project was succeeded by the "Operation and Management of Japan's Disease BioBank Intended for Utilization" of the Biobank Japan Project for Genomic and Clinical Research funded by the medical research and development promotion grants of the Japan Agency for Medical Research and Development, and BBJ's samples and information continue to be stored and provided.

As operational rules to promote BBJ itself and the utilization of samples and information of research participants that are stored at BBJ while respecting protection of personal information and complying with the "Ethical Guidelines for Human Genome/Gene Analysis Research," BBJ has established these guidelines.

II Operational Principles

The provision of samples and data collected at BBJ shall be conducted based on the following principles.

Principle 1: The results of research utilizing samples and data provided by BBJ are to contribute to various medical research and the realization of genomic medicine.

Principle 2: Samples and clinical information collected with support of public funds and data produced by utilizing such samples are to be shared widely.

Principle 3: The data is to be managed and provided appropriately in consideration of protection of personal information.

III Definition of Terms

The definition of terms used in these guidelines shall be as follows.

(1) BioBank Japan

A biobank established within the Institute of Medical Science, The University of Tokyo, under the Tailor-made Medical Treatment Program (abbr.: BBJ)

(2) BBJ Sample/Data Users

The Principal Researcher who utilizes samples/data stored at BBJ, and co-researchers who were registered at the time of application for data utilization by the Principal Researcher

(3) BBJ Storage Entrustors

The Principal Researcher and co-researchers of an organization that entrusts storage of samples of human origin to BBJ

(4) Principal Researcher

A researcher who is responsible for specific research (a researcher who applied for an ethics review of their research project by the ethics review committee of their organization and has obtained its approval, or a co-researcher who was listed in the ethics review application form)

(5) BBJ Samples

Human biological samples stored at BBJ (DNA, serum, tissue, etc.)

(6) BBJ Data

Data (the BBJ Clinical Information Data and the BBJ Prognosis Information Data) of research participants that are collected at 12 cooperating medical institutions and stored at BioBank

Japan under the “Tailor-made Medical Treatment Program (1st and 2nd)” and a new phase of the “Tailor-made Medical Treatment Program,” the NBDC Registered Data Correspondence Table, data of cooperating medical institutions (the BBJ Regional Information Data) and genomic data obtained by utilizing DNA of research participant origin

(7) BBJ Clinical Information Data

Clinical information data associated with the BBJ Samples. Items of clinical information collected at 12 cooperating medical institutions under the “Tailor-made Medical Treatment Program (1st and 2nd)” and a new phase of the “Tailor-made Medical Treatment Program” (list of clinical information items) are made public on the official website of BioBank Japan.

(8) BBJ Prognosis Information Data

Data of survival/death information and cause-of-death information obtained as results of survival surveys (surveys on hospital visits, resident records, and causes of death) conducted at 12 cooperating medical institutions under the “Tailor-made Medical Treatment Program (1st and 2nd)” and a new phase of the “Tailor-made Medical Treatment Program.” Since cause-of-death information utilizes data of vital statistics provided by the Ministry of Health, Labour and Welfare, there are limits on utilization of the information.

(9) BBJ Regional Information Data

Data of ID numbers of hospitals belonging to 12 cooperating medical institutions under the “Tailor-made Medical Treatment Program (1st and 2nd)” and a new phase of the “Tailor-made Medical Treatment Program” and information on locations of the hospitals that is produced based on the hospital ID numbers (including location categories, such as region, prefecture, and city/town/village)

(10) BBJ Genomic Data

Genotype data and sequence data that are produced by utilizing the BBJ Samples stored at BBJ

(11) BBJ Sample Derived Data

Data obtained by the BBJ Sample/Data Users by analyzing the BBJ Samples, and all data produced derivatively by them by processing the data. Data produced by collating the BBJ Sample Derived Data with the BBJ Data and individual data produced by processing the collated data are included in Secondary Data.

(12) Secondary Data

All individual data produced derivatively by processing the BBJ Data provided by BBJ. Deliverables and aggregate results are not included in Secondary Data.

(13) NBDC Registered Data Correspondence Table

A correspondence table of IDs for collating genomic data obtained by analyzing the BBJ Samples registered at the National Bioscience Database Center (NBDC) (NBDC Registered Data) with the BBJ Samples/BBJ Data

(14) BBJ Sample and Data Utilization Review Committee

A review committee established within BioBank Japan in order to conduct neutral and fair reviews with the aim of having the BBJ Samples and the BBJ Data utilized appropriately and effectively in accordance with the purpose of the program

(15) Storage Entrustment

Action of receiving and keeping samples from another organization for a certain period of time. Clinical information linked to the samples is not to be brought in to the Institute of Medical Science, The University of Tokyo, and storage space will only be provided for the information.

IV Scope of Application

All BBJ Sample/Data Users shall comply with these guidelines. Persons who have been BBJ Sample/Data Users since before the establishment of these guidelines are also subject to these guidelines.

V Utilization of the BBJ Samples and the BBJ Data

1. Qualification for Utilization

Persons who can apply for utilization as the Principal Researcher and co-researchers are limited to domestic researchers who have engaged in a relevant research (who belong to a university, public research institute, private company or any other similar organization and have research experience in a relevant research). Upon making an application, the applicants shall submit their past papers concerning research related to samples and data intended for utilization, and e-mail addresses issued by their organization.

Persons who can apply for utilization of cause-of-death information are limited to those who have made an application for utilization of survey data of vital statistics to the Ministry of Health, Labour and Welfare and obtained its approval in advance.

2. Rights of the Users

(1) Users of samples and data may publish research achievements utilizing the BBJ Samples and the BBJ Data freely as long as they fulfill the responsibilities of the users.

(2) The users may acquire intellectual property rights based on research achievements utilizing the BBJ Samples and the BBJ Data freely as long as they fulfill the responsibilities of the users.

3. Responsibilities of the Users

(1) The users shall utilize the BBJ Samples and the BBJ Data at their own responsibility and judgment on the quality, content, and scientific validity of the samples and the data.

(2) When utilizing the BBJ Samples and the BBJ Data, the users shall comply with the "Ethical Guidelines for Human Genome/Gene Analysis Research," "Ethical Guidelines for Medical and Health Research Involving Human Subjects" and other relevant guidelines, laws and regulations. That is to say, the users shall obtain review and approval of the ethics review committee of their organizations for utilization of the BBJ Samples and the BBJ Data. In an ethical review application form (research project plan), a description equivalent to the following item shall be specified.

<Example of a description in an ethical review application form (research project plan)>
◆Item to be included in an ethical review application form
Samples and data (XXX) of BioBank Japan are to be utilized for analysis of this research.

(3) The users shall comply with the following matters.

Basic matters to be complied with in utilization of the BBJ Samples and the BBJ Data
- Limit the users (only to the Principal Researcher and co-researchers for whom the application was made)
- Specify the purposes of utilization
- Do not use the BBJ Samples and the BBJ Data for any purpose other than the purposes for which the application was made
- Utilize the BBJ Samples and the BBJ Data only for research
- Do not identify any individual
- Do not provide the BBJ Samples and the BBJ Data to any person or organization other than the users for whom the application was made
- Do not sell the BBJ Samples and the BBJ Data

(4) The BBJ Sample/Data Users shall handle data safely by complying with the "BBJ Data Handling Security Guidelines (for Users)" in Appendix. Note that the required security level* may differ depending on the data. The BBJ Sample/Data Users shall also cooperate with an audit on the implementation status of security measures which audit is to be conducted by a third party at the request of the BBJ Sample and Data Utilization Review Committee or BBJ.

* [Security level]
Standard level [Type I] security is required in principle, but high level [Type II] security may be required through discussion with the BBJ Sample and Data Utilization Review Committee. For details of [Type I] and [Type II], refer to the "BBJ Data Handling Security Guidelines (for Users)."

When utilizing cause-of-death information of the BBJ Prognosis Information Data, the BBJ Sample/Data Users shall comply with, in addition to the "BBJ Data Handling Security

Guidelines (for Users),” the purposes of utilization, the place of utilization, and the measures for appropriate management specified in a written request (Form No.1) that is submitted to the Ministry of Health, Labour and Welfare.

(5) The BBJ Sample/Data Users shall establish a security control system in accordance with a required security level (Type I, Type II, etc.) and submit “BBJ Data Handling Security Guideline Checklist” to the Office of BioBank Japan for confirmation of compliance with the standards prescribed by BBJ.

(6) If data leakage or any other security accident occurs, the BBJ Sample/Data Users shall disconnect the device in question from the network and report to BBJ immediately. For subsequent handling of the accident, the BBJ Sample/Data Users shall promptly take measures in accordance with the instructions of BBJ.

(7) Upon completion of the utilization of the BBJ Samples and the BBJ Data, the BBJ Sample/Data Users shall cease utilization of or dispose of all samples obtained from BBJ and cease utilization of or delete all data obtained from BBJ (or in the case where all or part of the data is stored, all of the stored data) and shall report cease of utilization (and disposal) of the BBJ Samples and the BBJ Data by using a “BBJ Sample and Data Utilization Cease (and Disposal) Report.” For continuation of storage of the BBJ Samples, the BBJ Data, and the Secondary Data, as well as genomic data in the BBJ Sample Derived Data obtained by genomic analysis, refer to the separate item (V-4-(9)).

(8) When publishing analysis results containing samples and data provided by BBJ in a paper or any other publication, the BBJ Sample/Data Users shall specify that the samples and data were provided by BBJ, by listing papers specifying the overview of samples and information of BBJ as references or by any other similar means. For examples of references and descriptions, refer to the following sentences:

[Papers that should be listed as references for methods, etc.]

(1) Nagai A, Hirata M, Kamatani Y, Muto K, Matsuda K, Kiyohara Y, et al. Overview of the BioBank Japan Project: Study design and profile. Journal of Epidemiology 2017 MAR;27(3):S2-S8.

(2) Hirata M, Kamatani Y, Nagai A, Kiyohara Y, Ninomiya T, Tamakoshi A, et al. Cross-sectional analysis of BioBank Japan clinical data: A large cohort of 200,000 patients with 47 common diseases. Journal of Epidemiology 2017 MAR;27(3):S9-S21.

[Examples of citations]

“本研究に使用した試料及びデータ（の一部）は、ゲノム研究バイオバンク事業「利活用を目的とした日本疾患バイオバンクの運営・管理」の支援を受けているバイオバンク・ジャパンから提供を受けたものです。”

“The sample and data used for this research were provided from the BioBank Japan

Project that was supported by AMED."

(9) The BBJ Sample/Data Users shall acknowledge that BBJ may publish individual information or statistical information when disclosing the utilization status of its samples and data (examples of individual information to be disclosed: name of utilized samples and data, date of application, user's name and organization, and starting date of utilization).

(10) The BBJ Sample/Data Users shall acknowledge that BBJ may retain information on utilization of samples and data, such as user's information from the time of application to the time of report of utilization completion and information on accident occurrence, in order to utilize the information for disclosure of the utilization status of its samples and data.

(11) In the case where registration of individual genomic data/clinical information data in a public database is required upon publication of a paper, the BBJ Sample/Data Users shall discuss with BBJ in advance about items to be disclosed so that participants will not suffer a disadvantage.

(12) In the case of utilizing the BBJ Regional Information Data or any other case of conducting analysis for a specific region, the BBJ Sample/Data Users shall discuss with BBJ in advance about a conference presentation or paper submission so that participants or the region will not suffer a disadvantage.

(13) In the case of making a conference presentation or submitting a paper about achievements utilizing cause-of-death information of the BBJ Prognosis Information Data, the BBJ Sample/Data Users shall notify BBJ and obtain its approval in advance.

If a breach of any of the above provisions has been found, the utilization permission may be rescinded, and the breach may be disclosed on the website or by any other means. The above provisions apply not only to the Principal Researcher but also to co-researchers. The Principal Researcher is responsible for ensuring that co-researchers comply with these guidelines and the "BBJ Data Handling Security Guidelines (for Users)."

4. Procedures of Utilization

(1) The BBJ Sample/Data Users shall apply for utilization in accordance with the procedures of utilization application. In the case where several researchers belonging to different organizations intend to conduct joint research, information on each organization shall be included in the utilization application. Incidentally, each of such researchers may apply for sample and data utilization separately. In the case where the BBJ Sample/Data Users intend the BBJ Samples and the BBJ Data to be provided in a way that can be linked to the NBDC Registered Data (intend to use the NBDC Registered Data Correspondence Table), an application to that effect shall be made at the time of utilization application to BBJ. With respect to utilization of the NBDC Registered Data, the BBJ Sample/Data Users shall make a

utilization application to the NBDC.

(2) In any of the following cases, the BBJ Sample/Data Users shall develop a research project in which The University of Tokyo is listed as a joint research institute, through discussion with the person in charge in BBJ.

- In the case of intending to utilize the BBJ Regional Information Data
- In the case where users who utilize only the BBJ Data (those who do not receive the BBJ Samples) intend to utilize six items or more of clinical information data (excluding age, sex, and morbidity information for one disease) The number of items of clinical information data is calculated based on the list of clinical information items.
- In the case of intending to utilize cause-of-death information of the BBJ Prognosis Information Data

(3) For utilization of the BBJ Samples and the BBJ Data, the BBJ Sample/Data Users shall obtain review and approval of the ethics review committee of their organization and shall submit a copy of a written notification of permission from the head of their organization, at the time of making a utilization application; provided, however, that in the case where the ethics review committee has determined that the utilization is excluded from review, the BBJ Sample/Data Users shall submit a document or any other evidence to that effect.

(4) In making a utilization application, the BBJ Sample/Data Users shall submit "BBJ Data Handling Security Guideline Checklist" and other information and documents required by the BBJ Sample and Data Utilization Review Committee.

(5) The BBJ Sample and Data Utilization Review Committee shall judge whether utilization of samples and data is permitted or not.

(6) Information necessary for access to data will be provided after the BBJ Sample and Data Utilization Review Committee approves an application for utilization of the BBJ Samples and the BBJ Data. The users of the BBJ Data shall access the data by using the information at the place specified in "Appendix A to BioBank Japan Application Form for Sample/Data Utilization" as a place for utilization of provided samples/information. Information on categories of city/town/village, etc. in the BBJ Regional Information Data shall be utilized only within the Institute of Medical Science, The University of Tokyo, after approval of the medical institute providing the information.

(7) The BBJ Sample/Data Users shall report the status of utilization of the BBJ Samples/BBJ Data every August by using a "BBJ Sample and Data Utilization Cease (and Disposal) Report." At the same time, the BBJ Sample/Data Users shall also re-submit "BBJ Data Handling Security Guidelines Checklist"; provided, however, that in the case where the last day of August comes within six months from the starting day of utilization, the submission for August at that occasion is not required.

(8) In the case of intending to use samples and data in excess of the initial utilization period for the samples and data, the BBJ Sample/Data Users may continue utilizing the samples and data by, at least one month prior to the expiration of the initial utilization period, making an application for utilization continuation to the Office of BioBank Japan with a written notification of approval of ethical review from their organization (document indicating the approved research period) being attached and obtaining the approval of the Sample and Data Utilization Review Committee.

(9) Upon completion of the utilization of the BBJ Samples and the BBJ Data, or if the utilization has been terminated by the BBJ Sample and Data Utilization Review Committee on the ground of falling under "V-6. Actions Taken on the Ground of Misconduct (Including Suspicion)," the BBJ Sample/Data Users shall promptly cease utilization of or dispose of the BBJ Samples and cease utilization of or delete the BBJ Data and the Secondary Data and shall report cease of utilization (and disposal) of the BBJ Samples, and the BBJ Data and the Secondary Data to the BBJ Sample and Data Utilization Review Committee by using a "BBJ Sample and Data Utilization Cease (and Disposal) Report." In the case of intending to continue to store the BBJ Samples, and the BBJ Data and the Secondary Data based on data storage guidelines or other similar rules of their organization, the BBJ Sample/Data Users may do so by making a storage application to the Office of BioBank Japan by using a "BBJ Sample and Data Storage Continuation Application Form" and obtaining the approval of the BBJ Sample and Data Utilization Review Committee.

5. Expenses for Utilization

Actual expenses incurred in utilization of the BBJ Samples and the BBJ Data (such as expenses for materials needed for provision/sending of samples and expenses for media needed for transmission of data) shall be borne by the users.

6. Actions Taken on the Ground of Misconduct (Including Suspicion)

In the event of a suspected breach by the BBJ Sample/Data Users of any of the items in "V-3. Responsibilities of the Users" or the Security Guidelines, BBJ shall conduct an investigation into the alleged misconduct, and the BBJ Sample and Data Utilization Committee shall judge whether or not the alleged misconduct occurred based on the results of such investigation. If the BBJ Sample and Data Utilization Committee judges that misconduct occurred, or depending on the situation, even at the stage of suspicion of misconduct, any or all of the following actions shall be taken.

(1) The BBJ Sample/Data Users are to be ordered to cease their utilization of the BBJ Samples and the BBJ Data, and the permission to utilize the BBJ Samples that are being used and the

permission to access the BBJ Sample Derived Data, and the BBJ Data and the Secondary Data are to be rescinded.

(2) No new utilization application from a researcher who committed the misconduct will be accepted for a certain period of time. The period of time is to be determined by the BBJ Sample and Data Utilization Review Committee.

(3) A report is to be made to the head of the BBJ Sample/Data Users' organization as necessary.

Upon notice of utilization termination, the BBJ Sample/Data Users shall immediately cease utilization of, or delete, all of the BBJ Samples and the BBJ Data that have already been obtained, as well as the BBJ Sample Derived Data and the Secondary Data. The BBJ Sample/Data Users shall also report the status of utilization cease or disposal of data to the Office of BioBank Japan promptly by using a "BBJ Sample and Data Utilization Cease (and Disposal) Report."

VI Sample Storage at BBJ (BBJ Storage Entrustment Application)

1. Qualification for Utilization

Persons who can apply for Storage Entrustment of human samples are limited to domestic researchers who have engaged in a relevant research (who belong to a university, public research institute, private company or any other similar organization and have research experience in the relevant research). Upon making an application, the applicants shall submit information on the samples to be stored, relevant papers, and e-mail addresses issued by their organization. For utilization of Storage Entrustment, the Sample and Data Utilization Review Committee shall deliberate whether the facility of BBJ will be utilized appropriately and effectively in accordance with the purpose of the program.

2. Rights of the BBJ Storage Entrustors

The BBJ Storage Entrustors hold the ownership of stored samples. At the request of the BBJ Storage Entrustors, BBJ shall accept, store, and provide samples. In principle, expenses for acceptance, storage, and provision of samples shall be borne by the BBJ Storage Entrustors. Acceptance of samples the ownership of which is to be transferred to BBJ shall be discussed separately between the BBJ Storage Entrustors and BBJ.

3. Responsibilities of the BBJ Storage Entrustors

For entrustment of storage of specific samples at BBJ, the BBJ Storage Entrustors shall obtain review and approval of the ethics review committee of their organization and then obtain permission from the head of their organization. When providing samples to BBJ, the BBJ Storage Entrustors shall use the container designated by BBJ. The samples shall be in accordance

with the samples specified in the BBJ utilization application form. For storage at BBJ, the BBJ Storage Entrustors shall anonymize the samples.

4. Procedures of Storage Entrustment

(1) The BBJ Storage Entrustors shall confirm that they fulfill the responsibilities stipulated in "VI-3. Responsibilities of the BBJ Storage Entrustors."

(2) The BBJ Storage Entrustors shall arrange the timing of acceptance of samples and other settings with the Office of BioBank Japan.

(3) The BBJ Storage Entrustors shall apply for utilization in accordance with the procedures of the sample storage entrustment application. A copy of the research project plan (ethical review application), a copy of the written notification of approval, and forms of consent document and explanation document shall be attached to the application.

(4) The BBJ Sample and Data Utilization Review Committee shall judge whether acceptance of samples is permitted or not.

(5) The BBJ Storage Entrustors shall prepare samples to be stored and accompanying information.

(6) The BBJ Storage Entrustors shall send anonymized samples and necessary accompanying information in the way instructed by BBJ.

5. Provision of Stored Samples to a Third-party Organization

In the case where part or all of the ownership of samples that have been entrusted by the BBJ Storage Entrustors to BBJ and stored by BBJ is transferred to BBJ, and the samples are to be provided to another organization by BBJ, the provision of the samples shall be conducted in accordance with the procedures stipulated in "V Utilization of the BBJ Samples and the BBJ Data."

VII Procedures of Revision of These Guidelines

1. Procedures of Revision

Revision of these guidelines shall be conducted by the Office of BioBank Japan. The Office of BioBank Japan shall refer to an opinion of the Sample and Data Utilization Review Committee as necessary.

2. Proposal of Revision

The BBJ Sample/Data Users, the BBJ Storage Entrustors, persons providing samples, or persons thinking about utilizing samples and data may make a proposal of revision of these

guidelines to the Office of BioBank Japan if they consider that the revision will make provision and utilization of samples and data smoother. In doing so, they shall make a specific proposal or point out a specific part in question.

3. Examination of Revision Proposal

When receiving the above proposal, the BBJ Sample and Data Utilization Review Committee shall examine it promptly and provide an opinion on whether or not to accept or amend the proposal to the Office of BioBank Japan, and the Office of BioBank Japan shall conduct revision based on the opinion.

4. Publication and Application of Revision

When the content of revision is determined, the revised version of these guidelines shall be published on the official website promptly and shall apply after a certain period of time stipulated by the Office of BioBank Japan. The revised version of these guidelines apply also to persons who have made an application for data provision or data utilization and obtained permission prior to the start of its application unless the persons request otherwise.

VIII Others

1. Disclosure of Information on Data Provision Applications and Information on Data Utilization Applications

Among information on an individual application for utilization and provision of the BBJ Samples and the BBJ Data, information for which the applicant has given consent (refer to V-3-(9)) will be disclosed on the official website of BioBank Japan. With respect to other information that is not to be disclosed on the website, the BBJ Sample and Data Utilization Review Committee and staff of the Office of BioBank Japan shall not disclose the information to any third party.

2. Notification of Inaccurate Data, etc.

The Office of BioBank Japan shall accept and respond to notification from data users of inaccurate data in the BBJ Data. The same applies to notification from consenters and other similar persons about insufficiency of the method for obtaining consent, the possibility of fabricated consent or any other similar problem.