CARILION CLINIC INSTITUTIONAL REVIEW BOARD
Standard Operating Guidelines

Title: 3.7: Reviews Requiring Special Consideration: RESEARCH INVOLVING COLLECTION OF SPECIMENS OR DATA FOR A REPOSITORY OR DATABASE; RESEARCH USE OF SPECIMENS OR DATA FROM A REPOSITORY OR DATABASE	
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Primary Sponsor: Human Research Protections Office	**Approved By:** Director of the Human Research Protections Office

Objective:

To provide guidance for the procedure to establish a repository or database of specimens or data to be used for research and for the disbursement of such stored specimens/data to researchers.

General Description:

Obtaining (receiving or accessing) identifiable private information or identifiable specimens for research purposes constitutes human subjects research. Therefore, the collection and disbursement of specimens/data at Carilion Clinic for research or the operation of a repository/database using such specimens are subject to oversight by the Carilion Clinic Institutional Review Board (IRB). The IRB will review any application in which specimens/data in a repository/database may be accepted and shared and will ensure the repository application has adequate provisions to protect the privacy of subjects and maintain the confidentiality of data.

Definitions:

Research Repository/Database:
Any organized collection of retrievable, identifiable information pertaining to living humans that is intentionally maintained for use as an instrument for the conduct of research. The repository/database incorporates the name or identify of individuals, directly or indirectly, whose information or specimens are being maintained or stored. Such maintenance is intended for research purposes including, but not limited to future contact, e.g. recruitment for a research study; prospective research follow-up; or for data retrieval and analysis. A research repository/database also may be known as a registry, data set, tissue/specimen bank, or subject pool.

Human Subject Specimens:
- Bodily human materials, such as cells, mucosal and skin tissue, blood, urine, amniotic fluid, excreta and external secretions (including sweat), saliva, sputum, placenta tissue, organs, hair, nail clippings, teeth, dental plaque and calculus—if obtained through intervention or interaction with an individual or if identifiable
- Residual diagnostic and surgical human specimens, including specimens obtained for clinical patient care that would otherwise have been discarded if not used for research

Human Subjects Data:

- Private information such as clinical notes and medical information that can be identified with a specific individual, whether or not the information was specifically collected for research. This also includes private information provided for specific purposes by an individual, which the individual can reasonably expect will not be made public.
- Data obtained from voice, video, digital or image recordings
- Data obtained from surveys, interviews, oral histories or focus groups

Procedure:

The Carilion Clinic IRB is responsible for reviewing the collection, use, storage and re-use of all human specimens and data that are generated within, transferred to, or transferred from Carilion Clinic for research purposes. The IRB does not review the storage or management of specimens/data that are collected and stored as part of routine clinical care or hospital procedures. The IRB does not review the use or management of specimens/data sent to a Carilion Clinic investigator or employee for specialized analysis as part of a contractual agreement. IRB review and approval, however, is required prior to the use of these specimens/data for research purposes by a Carilion Clinic investigator.

Establishment and Operation of Repositories/Databases

A repository/database may be established within or outside Carilion Clinic. Repositories may be proposed, established, and maintained by individuals, groups, programs, departments, or institutes. A single investigator or a group of investigators may wish to pool research specimens/data from multiple research studies into a single specimen repository or database that could be accessed by others for further use.

Examples of outside repositories that a Carilion Clinic investigator may wish to utilize include the NIH, CDC, as well as laboratories managed by colleagues at other institutions.

Other conditions in which an investigator should consider the establishment of a repository are:

- When a clinical database is expressly designed for eventual research purposes, and that database incorporates research measures, or plans for group comparisons, the investigator should establish a repository prior to the collection of data for the purpose of research
- Databases maintained by physicians/investigators for record keeping of individual patients that will be accessed for research purposes for a single project must have IRB approval to do so. If it is expected that the data contained in the database will be accessed for multiple projects or by multiple investigators, a repository should be established.

Repositories/Databases Collecting Data from Multiple Sites

If the materials and data collected for a research repository/database are obtained from multiple sites, the IRB shall request the investigator provide to the participating sites:

- Repository/database application
- Sample consent form
- Recruitment materials
- Plan to require that investigators at other sites check with their local IRB regarding the requirements for local IRB review of the research repository. The PI shall require

documentation that local IRB review has been done before receiving materials and data from that site
- Reminder that investigators at other sites should check their institutional policies regarding the transfer of materials and data for research

The IRB shall require that the researchers responsible for oversight of the research repository have procedures in place to ensure that informed consent and HIPAA authorization have been obtained from the donors or their legal representatives before specimens are stored in the repository.

Sending Specimens or Data to an Outside Repository

If a Carilion Clinic investigator plans to send any identified specimens/data to an outside repository for storage for future research, then the Carilion Clinic IRB requires either documentation of local IRB approval at the database/repository site or written assurances from the keeper of the outside database/repository (i.e., an industry sponsor) that the subjects' privacy will be adequately protected. These assurances can be provided as part of a Data Use Agreement between Carilion Clinic and the institution or sponsor maintaining the database/repository or in a separate document. The assurances should reflect those required by HIPAA for data use agreements in 45 CFR 164.514(e)(4) - appropriate safeguards are to be used to assure used to ensure that protected health information is not used or disclosed inappropriately and no attempt will be made to identify the individuals to whom the information pertains, or to contact such individuals except as otherwise stipulated in the informed consent/HIPAA authorization form. The wording of the assurance may vary depending upon the specific characteristics of the database/repository and other circumstances.

IRB Review of Repository/Database Applications

Before a repository/database can be established to store specimens or data intended for research purposes, the IRB must review and approve an application submitted by a qualified investigator who will exercise control over the repository. The application must describe the conditions under which specimens/data may be collected and the conditions under which specimens/data may be accessed by other researchers. The level of Carilion Clinic IRB review and oversight is based on the level of risk the study poses. Specimen/data research risks potentially include one or both of the following:
- The risk of harm from procedures used to obtain specimens/data
- The risk associated with the loss of privacy and confidentiality due to personally identifiable information that may be associated with specimens/data

The IRB will assess the repository/database to assure that adequate measures have been taken to protect the confidentiality of subjects. This review will include:

- The type of specimens or data to be banked
- Whether the specimens/data are identified or coded
- What procedures are in place to de-identify the specimens/data
- Whether the collection of specimens/data requires interaction with human subjects
- Whether the specimens/data 'on the shelf' at the time the proposal is initiated
- Whether informed consent be required
- Who will manage the repository
- How and where will the specimens/data be stored and released
- What will happen to the specimens/data should the subject withdraw informed consent, or the investigator should leave the Institution

- Who owns the specimens/data

IRB Application Types:

Human Subjects Research Study Application
Specimens/data to be collected prospectively for pre-defined research purposes only in connection with a single IRB-approved application. The usage might involve specific testing of tissue or a single analysis of data. In most cases, this type of collection would not be considered a research repository/database.

Also, this application must be submitted if specimens/data are to be taken from an IRB-approved repository/database for a specific research project.

Establishing a Prospective Data or Specimens Research Repository Application
Specimens/data to be collected prospectively or retrospectively for undefined future research purposes that will be shared, used again, or stored for research purposes should be stored in a research repository/database:

- If the specimens/data are collected in conjunction with a research study and are intended for storage, the investigator should submit (1) *Human Subjects Research Study Application for the separate research study* and *(2) Establishing a Prospective Date or Specimens Research Repository Application.*
- If the specimens/data are collected solely for a research repository/database, then submit a *Establishing a Prospective Date or Specimens Research Repository Application.*

Determination of Human Subjects Research Application
If the specimens/data are de-identified (none of the 18 HIPAA identifiers) or unlinked, and the investigator believes the project qualifies as non-human subjects research, then this application should be submitted. The specimens must be provided in a de-identified manner.

Informed Consent & HIPAA for Repository/Database Applications
Informed consent and HIPAA authorization must be considered at the time of initial approval of a repository/database. Informed consent information describing the nature and purposes of the research should be as specific as possible. For guidance on consent forms used in database/repository research, see the *Consent To Take Part In A Biorepository Research Study* template.
Included among the basic elements of informed consent, there should be a clear description of the following:

- How the privacy and confidentiality of donors will be protected and maintained in the collection, storage and distribution of their materials and data
- The specific types of research, both present and future, to be conducted
- Allowances made for unidentified use of specimens vs. identified use of specimens
- Whether donors will be contacted for future research participation
- A statement indicating that there is no cost to the subject or their insurance company for the storage and use of specimens
- The conditions under which specimens and data will be released to recipient-investigators
- Allowing commercial use of specimens
- Procedures for protecting the privacy of subjects and maintaining the confidentiality of data
- Whether specimens will be stored indefinitely, and if specimens could be disposed of at the discretion of the investigators

- The process for subjects to contact the researcher if they choose to no longer have their specimens stored, and what will happen to those specimens if the subjects withdraw
- Whether the results of research done with the stored materials and data will be made available to the donors and their legal representatives and if so, under what circumstances and by what means. This section should address new information that may be helpful to subjects, and disclosure of information that a subject may choose not to know.
- That there are no provisions for compensating donors who provide materials and/or data if future research leads to commercial products or services

When the repository contains genetic specimens/data, the IRB will verify that the Carilion Clinic IRB genetic template language has been included within the informed consent documents for the specific study in which the repository will be used, as well as any mandated disclosures.

Re-consent or de-identification of samples may be necessary if the proposed research exposes the subjects to greater risk than previously contemplated.

HIPAA: If HIPAA authorization is required from a donor-subject, the use of standard HIPAA language will be necessary. This language is contained in the Carilion Clinic IRB consent form template. The Privacy Rule does not permit authorization for future unspecified research. However, authorization may be obtained to create and maintain a research repository/database and no authorization would be required for subsequent use or disclosure of de-identified data or of a limited dataset with a data use agreement. The authorization to create and maintain a research repository can be done in a separate authorization document or it must have a separate signature section if combined with the informed consent document.

The Privacy Rule does not apply if the repository or collecting site will not use or disclose any of the 18 identifiers that must be removed to create a de-identified dataset, and Carilion Clinic has no knowledge that the information could be used to identify the patient. Patient authorization would not be required in such a case. Carilion Clinic may have one of its employees or a third party de-identify the PHI before use or disclosure of the information for research purposes. This process of de-identifying PHI is treated as a covered entity "health care operation," which may be done without the individual's authorization. If Carilion Clinic as a covered entity uses a third party (non-employee) to de-identify the information, it must first have a business associate agreement in place with that third party. This third party may be the researcher; this means that the PHI may be released to a non-employed researcher for the purpose of de-identification only if the covered entity has a business associate agreement in place with the researcher.

If the repository or collecting site is only using or disclosing a limited data set, i.e. a data set that does not contain any of the 16 identifiers that must be removed to create a limited data set, that data may be used and disclosed without authorization as long as there is a data use agreement with the recipient. A data use agreement is a written understanding between Carilion Clinic and the recipient of the limited dataset that the recipient will not identify the subject that also meets the other requirements specified in the regulations. The use of a limited data set is often sufficient for repositories, because it can include complete dates and geographic identifiers, such as city, state and zip codes.

Pediatric Research

Pediatric research with stored biological materials presents unique issues because children cannot consent to their own research participation. When children reach maturity, they may not

agree with their parents' research decisions. There is no consensus about the scope of parental authority with respect to the research use of children's biological materials. The principal investigator should be aware of the importance of obtaining informed consent from donors who were minors at the time the materials or data were collected for the repository, once the minor reaches the legal age of consent.

Level of IRB Review

Full Board Review: A study proposing to collect specimens/data using procedures that pose greater than minimal risk to subjects must undergo full committee review by the Carilion Clinic IRB. Examples include:

- Specimens will be collected using procedures posing greater than minimal risk as part of a larger application such as a clinical trial or intervention study
- Greater than minimal risk procedures will be used to obtain additional specimens/materials in excess of that required for diagnosis or treatment.
- When the repository contains genetic specimens/data are being collected with the intent of future genetic analysis.

Expedited Review: The IRB may determine the activity qualifies for expedited review according to 45 CFR 46 110. Before the application can be considered for expedited review, the IRB must determined that a) the research does not involve the risk of exposing the identity of sample donors and sensitive information about a rare trait/disorder; b) the repository/database has an adequate policy concerning confidentiality; c) accidental disclosure of results would pose only minimal risk to participants d) the research poses no risk of community or cultural harm e) the research meets the criteria of minimal risk. Categories of research that may qualify for expedited review include:

- Research involving previously collected specimens coded by a third party such that the code cannot be broken if there is some risk of exposing the identity of donors;
- Research involving prospectively collected anonymous or unidentifiable specimens;
- Research involving prospectively collected specimens coded in such a way that the code could be broken on request;
- Research involving anonymous or unidentifiable specimens collected expressly for research purposes;
- Research involving coded specimens collected expressly for research in such a way that the code cannot be broken.

Exempt Review: The IRB may determine an access application qualifies for an Exempt research determination as defined in 45 CFR 46.101(b) if:

- The research involves anonymous or unidentifiable specimens that were previously collected or
- The research involves previously collected specimens coded by a third party such that the code cannot be broken, so long as the research meets the criteria of minimal risk and does not involve a risk of exposing the identity of sample donors and sensitive information about them.

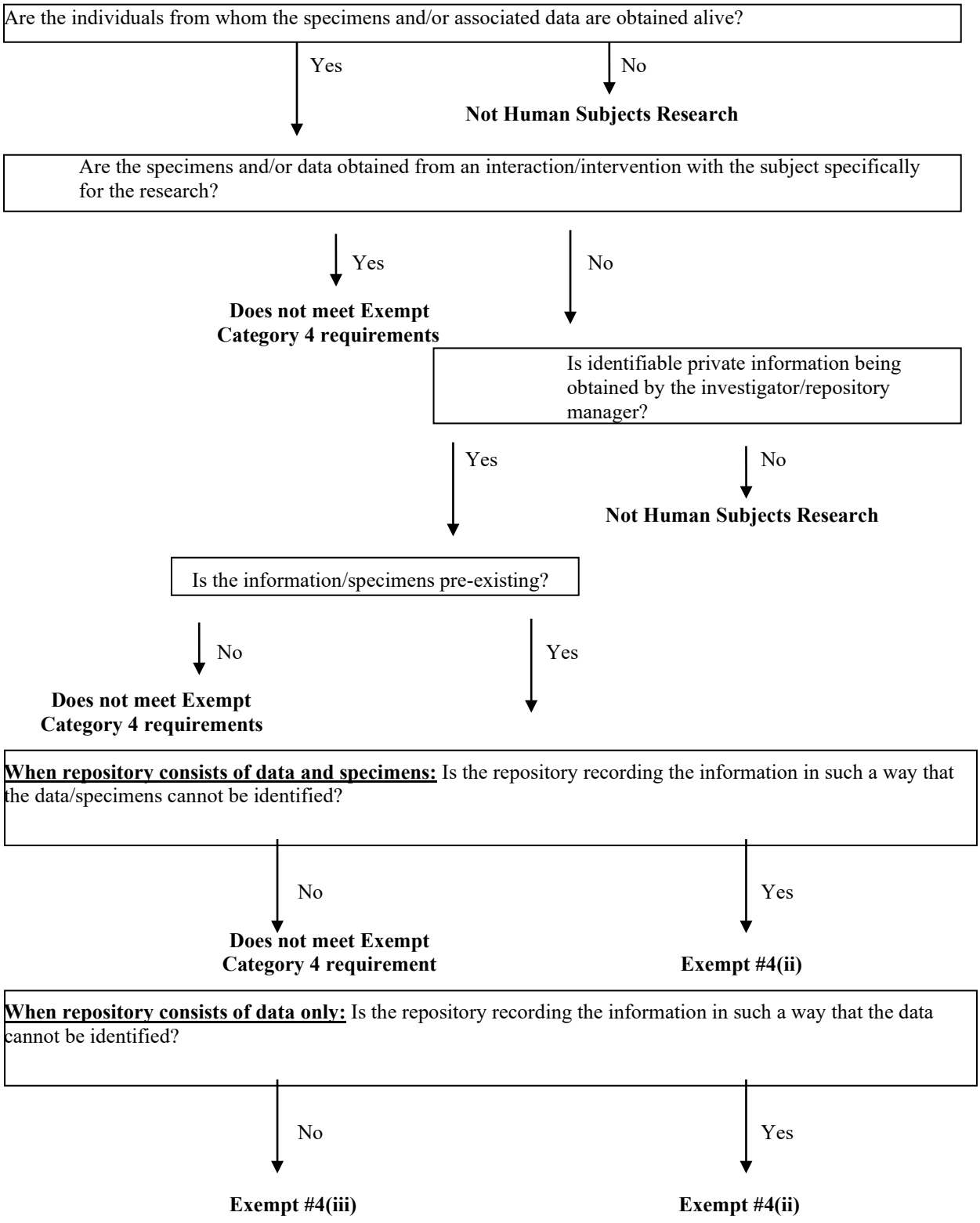
See Flow Charts 1 & 2 at the end of this guideline for further information on determining whether an activity constitutes human subjects research or does not qualify as human subjects research.

Non-Human Subjects Research: Researchers often receive specimens/data from banks and repositories that are either de-identified (none of the 18 HIPAA identifiers) or coded. Studying

human specimens/data without identifiers protects the identity of the subject/donor without compromising the goals of meaningful research. The definition of human subjects does not apply to research involving unidentified, unlinked or, under specific conditions, coded specimens/data. The IRB may determine that the use of de-identified specimens/data in storage that will be released for use in research does not qualify as human subjects research. The IRB assesses the study procedures to ensure that specimens are truly unidentified or unlinked or, if the research involves only coded specimens, that adequate subject privacy protection measures are in place.

Flowchart 1
COLLECTION AND BANKING OF SPECIMENS AND/OR ASSOCIATED DATA FOR RESEARCH

This flowchart was designed to help illustrate when the **collection and banking** of specimens and/or associated data for research is considered human subject research under the HHS Human Subject Protection Regulations, 45 CFR part 46and when it meets the criteria for Exemption #4 [45 CFR part 46.101(b)].



Flow Chart 2

RESEARCH USE OF SPECIMENS AND/OR ASSOCIATED DATA

This flowchart was designed to help illustrate when the research **use of specimens and/or associated data** is considered human subjects research under the HHS Human Subject Protection Regulations, 45 CFR part 46 and when it meets the criteria for Exempt #4 [45 CFR part 46.101(b)].