NMDP Institutional Review Board

Human Subjects Protections Guidance

Does Your Project Require IRB Review?

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Quick Reference

Purpose: Help investigators determine whether or not an activity is human subjects research requiring IRB review.

Two Key Questions:

1) Is the activity "research"? [45 CFR 46.102(l)]
2) Does it involve "human subjects"? [45 CFR 46.102(e)]

1. Introduction

Investigators studying, using, or analyzing information or biospecimens obtained from living individuals must determine whether their activity involves human subjects research requiring IRB review. If uncertain, submit a **Human Subjects Research Determination xForm** in IRBManager for NMDP IRB staff review (see IRBManager instructions on the NMDP IRB website).

2. Is the Activity Research?

2.1 Definition of Research

Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge [45 CFR 46.102(l)]. Systematic investigation employs a method for data collection and analysis (often with a hypothesis or predefined objectives).

2.2 Generalizable Knowledge

Generalizable knowledge is knowledge that can be used to draw conclusions beyond the specific study population (e.g., inform policy or practice). This includes knowledge that:

- Is applied to individuals, programs, or sites not included in the study
- Informs future implementation, scale-up, or decision-making
- Supports broader conclusions about effectiveness, adoption, or outcomes
- Is intended to contribute to a body of scientific knowledge

Knowledge is considered generalizable even when findings are shared only within a defined network (e.g., NMDP transplant centers). If findings from a subset of sites are intended to inform other sites, it represents extension beyond the study population.

Activities primarily intended for internal management (program evaluation, QA/QI, audits, or marketing) generally are not research, unless there is a clear intent to contribute to

generalizable knowledge. Activities limited to a single, specific program or operational setting and intended only to improve that program are generally not research. Activities are generally not research when ALL the following apply:

- Purpose is internal program improvement only
- Conducted as part of routine operations
- Findings are used only within the evaluated setting
- No intent to generalize beyond the people or sites participating in the activity being evaluated
- Does not test a hypothesis or research question

Reference OHRP Quality Improvement Activities FAQs

In certain cases, a quality improvement project may constitute human subjects research. For example, if a project involves introducing an untested clinical intervention for purposes which include not only improving the quality of care but also collecting information about patient outcomes for the purpose of establishing scientific evidence to determine how well the intervention achieves its intended results, that quality improvement project may also constitute human subjects research under the HHS regulations.

2.3 Program Evaluation vs. Research (Quick Comparison)

Dimension	Program Evaluation	Research
Intent	Evaluate a specific existing NMDP program or its community to inform that program	Generate knowledge intended to apply beyond the specific program/community
Design	Assess/process-improve NMDP processes, products, or community experience	Answer a scientific question or test a hypothesis to contribute to scientific knowledge
Population	Individuals affiliated with a specific program	Sample sized to meet endpoints; population defined by study aims
Dissemination	Share results with stakeholders/participants; may publish as models/strategies/tools without claiming generalizability	Disseminate via research publications/grants; intended to contribute to generalizable knowledge

Note: The mere intent to publish a program evaluation does not, by itself, make it research, so long as the publication clearly describes it as a program evaluation and does not claim generalizable inference.

2.4 Examples

Example: Patient Registry interviews to improve Patient Advocacy services; not intended for publication.
Determination: Not research (purpose is program/process improvement).

Example: Analyze HLA haplotype frequencies and estimate match rates for a country; results will inform the clinical community and be published.
Determination: Research (intent is to generate new knowledge with broader applicability).

Example: Evaluate software to identify poor prognosis searches; goal is to decrease search time for internal workflow.
Determination: Not research (process improvement).

3. Does the Research Involve Human Subjects?

If the activity meets the definition of research, then determine whether it involves human subjects.

3.1 Definitions

OHRP definition [45 CFR 46.102(e)(1)-(7)]:

- A human subject is a living individual about whom an investigator conducting research: (i) obtains information or biospecimens through intervention or interaction with the individual and uses, studies, or analyzes them; or (ii) obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

FDA definitions:

- 21 CFR 56.102(e): A human subject is an individual who participates in research, as a recipient of the test article or as a control.
- 21 CFR 812.3(p): For devices, a subject is a human on whom or on whose specimen an investigational device is used, or as a control.

3.2 Key Terms

Intervention: Physical procedures (e.g., venipuncture) or manipulation of the subject or their environment for research purposes.

Interaction: Communication or interpersonal contact with the subject (e.g., face-to-face, mail, email, phone, or other modes).

Private information: Behavior in contexts where an individual can reasonably expect privacy (i.e., no observation or recording is taking place) or information provided for

specific purposes that the individual expects will not be made public (e.g., medical record).

Identifiable: One or more data elements that, alone or combined with other reasonably available information, can identify an individual.

3.3 NMDP Donor and Patient Identifying Information

Per NMDP SOP-00106 *Confidential Information Standard Operating Procedure (Unrelated Donor/Patient Confidentiality)*: **Personal Information** includes any information that identifies, describes, or is capable of being associated with a particular individual (e.g., name, address, birth date, phone, government IDs, SSN, passport, emails, financial accounts, passwords, employment information).

Donor-Identifying Information includes personal information of registrants/donors and transplant-related details (e.g., registry, donor center, collection date/month, location, gender, age, ABO/Rh, HLA type, IDM results, health history, conditions, tests, medications, treatments, photographs). Country of origin for a donated product is not included.

Patient-Identifying Information includes personal information of any patient/recipient and transplant-related details (e.g., managing transplant center, location, gender, age, ABO/Rh, HLA type, health history, conditions, tests, medications, treatments, photographs). Destination country for a donated product is not included.

Reference FRM-00158 *Algorithm Analysis* to help determine if NMDP donor is a human research subject on a recipient research protocol.

3.4 Examples

Example: Evaluate costs and utilization of HCT vs. no HCT using claims data with no patient identifiers; results published in aggregate.
Determination: Research that does NOT involve human subjects (no interaction/intervention and no identifiable private information).

Example: Characterize DPB1 allele; donors provide buccal swabs; results published.
Determination: Research involving human subjects (interaction and intervention occur).

4. Secondary Research

Secondary research reuses information or biospecimens originally collected for another research **or** non-research activity. Sources may include donor/patient registries, the Center for International Blood & Marrow Transplant Research (CIBMTR) database, or investigator databases. Information may be identifiable, de-identified, or coded.

4.1 Research Data Originally Collected Under Consent

To use data from a prior research study, confirm subjects consented to sharing under the parameters of the secondary research. If not: (a) amend the original protocol/consent if within scope and feasible; (b) obtain de-identified data; or (c) propose a new project and determine if it is human subjects research.

4.2 De-identified Data

Using de-identified data (removing all identifiers and any links) reduces privacy risk. Secondary research using de-identified data is not human subjects research. If direct identifiers or links are required, the data is not considered de-identified; therefore, submit an Initial Application for IRB review and justify the necessity to use identifiable data.

HIPAA de-identification guidance: https://www.hhs.gov/hipaa/for-professionals/privacy/special-topics/de-identification/index.html#protected

4.3 Examples

Example: Seeking to better understand the geographical distribution of post-allogeneic hematopoietic cell transplant (HCT) outcomes by assessing the potential unmet social needs areas. CIBMTR dataset will be merged with other publicly available zip-code datasets.
Determination: Research that does NOT involve human subjects (the data obtained and liked for the purposes of this research is not identifiable private information as the investigator will not be able to readily ascertain the identity of the participants).

Example: Study is looking at whether variation in HLA genes may impact infection with CMV in healthy individuals. Researchers will use a de-identified dataset (with no direct identifiers and no access to any linking code) from 366,481 donors who were typed for both CMV and HLA to examine whether HLA type affects CMV infection.
Determination: Research that does NOT involve human subjects (the dataset is de-identified and investigators cannot readily ascertain the identity of individuals).

4.4 Anonymous Research Using Unused Donor Products, Cord Blood Products, or Donor Specimens

Per NMDP Policy PL-00062 *Policy for Disposition of Donor Products, Cord Blood Units and Specimens*, anonymous research on donor products, cord blood products, or donor specimens is permitted only when there is absolutely no identifying link to the donor through which an investigator can readily ascertain donor identity, including collection date or other means. (Refer to the policy for additional requirements regarding use for anonymous research.)

4.4 Coded Data

“Coded” means identifiers are replaced with a code and a key exists that can link back to identities.

OHRP Guidance: https://www.hhs.gov/ohrp/coded-private-information-or-biospecimens-used-research.html

OHRP considers private information or biospecimens individually identifiable when investigators can link them to specific individuals directly or via a code. When investigators cannot readily ascertain identity (e.g., an agreement or SOP prohibits release of the key until individuals are deceased), OHRP does not consider the activity to involve human subjects.

5. Secondary Research Involving Data Linking

Data linkage combines information about individuals from different sources to support research (e.g., linking external datasets to CIBMTR). NMDP and CIBMTR comply with privacy/confidentiality regulations and do not release protected health information (PHI) or personally identifiable information (PII).

When PII is required to link datasets, follow special procedures, including use of an honest broker (a party that provides de-identified data to investigators). If the source is a research study, ensure consent permits data sharing outside that study. Requests to disclose PII to link CIBMTR data to an external source must be approved by the NMDP IRB. Other institutional restrictions may apply.

6. Secondary Research that is Exempt

Some human subjects research qualifies as Exempt under 45 CFR 46.104. Submit an Initial IRB Application to the NMDP IRB for an exempt determination before starting. Exempt research does not require ongoing IRB oversight unless changes impact the determination. Exempt determinations are made by the NMDP IRB Administrator or Chair.

Regulatory text: https://www.ecfr.gov/current/title-45/subtitle-A/subchapter-A/part-46/subpart-A/section-46.104

Exempt category 4(ii) applies to secondary research using identifiable private information or identifiable biospecimens where information is recorded in a manner so that subjects cannot be readily identified directly or via identifiers, and investigators do not contact subjects and will not re-identify subjects.

6.1 Examples

Example: Cost-effectiveness analysis of double cord blood vs. haploidentical related bone marrow using existing CMS/commercial claims and clinical trial data; no subject contact; datasets accessed without specific identifiers; reports include only de-identified aggregate data.
Determination: Exempt under 45 CFR 46.104(d)(4)(ii) (secondary research; identities not readily ascertainable; no contact; no re-identification).

7. Modern Sources: Social Media and AI

7.1 Social Media

Public posts/no interaction: Passive analysis of public posts recorded only as aggregated data or paraphrased quotes may not involve human subjects or may qualify for Exempt category 4 when retained fields could enable identification. Avoid verbatim quotes that enable reverse lookup. Consider ethical implications where use could affect willingness to post.

Non-public spaces or direct messaging: Access to private groups or direct contact may constitute interaction and involve identifiable private information. IRB review may be required if the project qualifies as “research” as defined by the federal regulations.

Recruitment: Social-media advertisements are the first step in the recruitment and informed consent process and require IRB review for human subjects research.

7.2 Examples

Example: An investigator analyzes public comments on NMDP’s Facebook page to assess overall sentiment about donor registry messaging. Results are reported as aggregate trends (e.g., percent positive vs. negative sentiment). No usernames, quotes, or identifiers are retained.
Determination: Not human subjects research (no interaction or intervention and data is not considered private information)

Example: An investigator joins a private Facebook group for transplant recipients and systematically collects posts to study patient experiences with donor searches. The group is not publicly accessible. Posts may contain identifiable private information.
Determination: Human subjects research (involves identifiable private information and/or interaction))

7.3 Artificial Intelligence (AI)

Model development/validation that obtains, uses, studies, analyzes, or generates identifiable private information about living individuals is human subjects research [45 CFR 46.102(e)]; IRB review is required, if the project is considered research.

If a dataset is truly synthetic (no record corresponds to a real person) with documented methods showing a very small re-identification risk, the activity typically does not involve human subjects; IRB review is not generally required.

Administration of research (e.g., data analysis support, recruitment, transcription) may fall outside IRB purview, but investigators should address ethical safeguards: describe AI’s role, validate systems, evaluate bias/fairness, and address privacy.

AI as the intervention (e.g., clinical decision support or AI-enabled medical devices) may require IRB review depending on the development stage (discovery, translation, deployment) and regulatory oversight.

7.4 Examples

Example: An investigator develops a machine learning model using NMDP donor and patient data (e.g., HLA type linked to clinical outcomes) to predict transplant success. The dataset includes coded identifiers that the research team can link back to individuals.
Determination: Human subjects research (uses identifiable private information)

Example: A research team trains and tests an AI model using a fully synthetic dataset generated to mimic NMDP transplant data, where no record corresponds to a real individual
Determination: Not human subjects research (no real individual's data are used)

8. OHRP Human Subjects Regulations Decision Charts

NMDP IRB follows OHRP decision charts for all human subjects research regardless of funding.

Contact the IRB

Questions? Email IRBStaff@nmdp.org or call 1-800-526-7809.