

ISSUES TO BE ADDRESSED WHEN CONDUCTING EXEMPT REVIEW

University of Kentucky Educational Resource

Making a determination that a study is eligible for exemption is not always an easy task. Below are examples of issues that the IRB reviewers should consider when conducting the Exemption Review.

Additional Regulatory Protection for Children and Prisoners

Certain research activities can **not** be exempt because additional protection has been granted by federal regulations for vulnerable populations. The categories of research that can **not** be exempt are as follows:

1. Research involving survey or interview of children;
2. Research involving the observation of public behavior of children unless the investigators do not participate in the activities being observed;
3. Research involving prisoners.

All Research Activities Must Fit Within Six Federal Categories

For a study to be eligible for exemption **all** of the research activities must fit in one or more of the six categories listed below. In some cases, all but one of the activities will fit in the categories. For example, sending a mail questionnaire on a non-sensitive topic which requests that the survey be returned without identifiers would appear to be a methodology that meets category 2 below. However, if the researcher obtained the list of subjects and their addresses from private records (e.g., student transcripts or medical records), then the research might not be eligible because it does not meet the conditions of category 4 listed below.

Risk Assessment Considerations

Research eligible for exemption usually involves little or no risk to subjects. Some reviews apply the “minimal risk” standard when conducting exempt review. When determining “minimal risk” the IRB reviewer must first identify all the risks associated with the study. Department of Health & Human Services defines “minimal risk” to mean “the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests” [45 CFR 46.102(2)(i)].

Exemption Applications that Do Not Meet the Definition of Human Research

The exemption process is further complicated because occasionally an activity that is sent to the IRB using an Exemption Application Form does not meet the federal definitions of “research” or “human subject”. These definitions are included in the UK “When do activities involving human subjects need Institutional Review Board (IRB) review and approval?” guidance document on <http://www.research.uky.edu/ori/human/guidance.htm>.

In analyzing whether activities involve human subjects, it is important to focus on what is being **obtained** by the investigators. If the investigators are not obtaining either data about living individuals through intervention or interaction, or identifiable private information, then the research

activity does not involve human subjects. Reviewers should contact ORI staff if they think that might be the case in a specific application.

Guidance for Applying the Six Exemption Categories

- (1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular or special educational instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.**

The IRB reviewer has to consider whether the proposed activities constitute “normal educational practice” and if the setting is a “commonly accepted educational setting”. For example, a study to develop an innovative method for teaching math in the second grade would be eligible under this exemption provided the curriculum development methods reflected normal educational practices. Typically the educational setting would be a classroom. However, teaching students to drive in a driver’s education class or teaching children or adults to cook in a formal cooking class could be considered a “normal educational setting”. The IRB reviewer can contact one of the IRB College of Education representatives for guidance regarding whether the research is occurring in an “accepted education setting” or whether it involves “normal educational practices.”

This category does not apply to Food and Drug Administration (FDA) regulated research.

- (2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects financial standing, employability, or reputation. For Veteran Affairs Medical Center (VAMC) research, damage to the subjects’ insurability must also be taken into consideration.**

Several research activities are addressed in this category. These activities are:

- use of educational tests;
- survey procedures;
- interview procedures; and
- observation of public behavior.

The category defines two conditions, that when both exist, exclude the activities from consideration for exemption. The study can be exempt if the activities only meet one of the conditions below:

- the information gathered during these activities can be linked to the subject, either directly or by some coding system if the researchers can access the codes
- should a third party gain access to that information, the subject would be placed at risk. The risk can be for criminal or civil liability or can be the risk of damaging a subject’s financial standing, reputation, employability, or insurability.

An example would be a survey randomly sent to individuals selected from an employment roster. The survey asks the subjects their opinions on the managerial skills of their supervisors, without naming the supervisors. The investigator wants a 95% response rate so although she does not ask the subject's name or social security number, she codes the questionnaires so she can tell who responds. After a certain period of time, she sends a second questionnaire to those randomly selected individuals who did not respond to the first request. Also, she plans to keep the code so that she has the option to follow up with subjects if she needs clarification regarding their responses.

Since there is a code that links data with names, breach of confidentiality is possible even though it might be unlikely to occur. That could potentially place the employee's job security and financial standing at risk. Consequently, this study would not be eligible for exemption.

If, however, there is no risk associated with a subject's responses, having identifiers will not disqualify a study from exemption. There are many studies that ask for information that, if disclosed, would not put a subject at any type of risk. A study could have identifying information on the survey or questionnaire and still be eligible for exempt review provided disclosure of subject responses would not put subjects at risk.

This exemption is narrowed in scope by 45 CFR 46 Subpart D's additional protections for research involving children. Where children will be involved as research subjects, the use of survey or interview procedures is eliminated from this exemption, and so is any research involving the investigators participating in the activity being observed. OHRP has also stated that observing a classroom does not constitute public behavior and is not permitted for this exempt category.

Audio taping in exempt research

The Department of Health & Human Services Office of Human Research Protection (OHRP) has stated that "... even when audio taping is done, a research project involving non-prisoner adult human subjects may meet the criteria for exempt #2 if the information is not sensitive in nature and could not reasonably place the subject at risk of criminal or civil liability or be damaging to the subjects' financial standing employability or reputation ...".

This category does not apply to FDA regulated research.

- (3) Research involving the use of education tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under category (b) of this section, if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.**

This category can be confusing and actually applies to two very different criteria.

Item (i) of this category includes the research procedures previously identified in category 2 (i.e., use of educational tests, survey procedures, interview procedures, and observation of public behavior). However, this category differs from the previous one in the situations to which it applies. If the population targeted for the research activities are elected or

appointed officials or candidates running for public office, the research qualifies for exempt review.

OHRP has provided guidance on what constitutes public officials. Public officials could include mayors, governors, school superintendent, school board members, police chief and others appointed by a state official. Public officials would not include public employees such as teachers or police officers.

An example of research that fits this category would be a survey administered to town mayors within a county that contains questions that might expose information which the public might not support. The PI can plan to report that data, identifying the mayors that participated in the study and even identify how certain mayors answered specific questions, and still qualify for exempt review. Public officials or candidates running for public office give up their right to confidentiality in lieu of the public's "right to know."

The second part of this category (ii) addresses the use of educational tests, surveys, interviews, or observation of public behavior to collect data for specific federal programs conducted or supported by the Department of Justice or data collected for the Institute of Education Sciences which includes the National Center for Education Statistics of the United States Department of Education. These agencies have specific programs that create data bases which are then protected by law from ever being accessed by anyone other than those federal agencies. No officer or employee of the Federal Government, and no recipient of assistance under the provisions of this category is allowed to use or reveal any research or statistical information furnished under this category by any person and identifiable to any specific private person for any purpose other than the purpose for which it was obtained. Data collected for these programs will be immune from legal process and cannot, without the consent of the individual concerned, be admitted as evidence or used for any purpose in any action, suit or other judicial or administration proceeding.

The only circumstance in which an exemption application would be submitted to the University of Kentucky's IRB for consideration utilizing part (ii) of the category would be if a PI from the University of Kentucky was issued a grant to conduct research involving specific programs by the Department of Justice or the National Center for Education Statistics.

This category does not apply to FDA regulated research.

(4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

Clarification on Existing Data

According to the Office for Human Research Protections (OHRP), to qualify for this exemption criteria the data, documents, records, or specimens must be in existence at the time of IRB review. OHRP interprets the term "existing" to mean that all of the data, documents, records, or specimens to be used in the research are in existence prior to IRB review and were collected for purposes other than the proposed research. The IRB reviewer must assure that the investigator has shown that all of the data to be collected under this category are currently in existence at the time of IRB review.

Based on the federal definition of “existing data,” research conducted on biological or pathological specimens obtained **prospectively** and taken strictly *for research purposes* **does not** qualify for exempt review.

Based on the federal definition of “existing data,” research conducted on biological or pathological specimens obtained **prospectively** from future *discarded clinical samples* **does not** qualify for exempt review. A prospective study does not meet the definition of “existing”. Also, if there is any “prospective” component of the research procedures, the research will not qualify for exempt review (for example information taken from existing records which will be compared to information to be collected at some future date).

Publicly Available or Subject Identifiers

IRB Reviewer must determine if:

1. the data, documents, records, or specimens are collected from publicly available sources **or**
2. of the information is recorded so that subjects can be identified directly or through identifiers linked to a subject.

If the collection of data, records, or specimens meet either of these two conditions, the research cannot be exempt.

What is meant by “publicly available resources”? This language in the regulation was intended to apply to public sources of data, such as local telephone directory information. For example, student records which are covered by the Family Educational Rights and Privacy Act (FERPA) are not public records. The meaning of this language with respect to human tissue specimens is widely debated. Although there are organizations that make human cells and tissues broadly accessible to the research community, these materials are not usually available to the public at large and are not generally considered to be publicly available.

What is meant by “identifiers linked to the subjects”? Identifiers can include names, social security numbers, medical record numbers, or other codes that permit specimens or data to be linked to living individuals and perhaps also to associated medical information.

For example, biological or pathological samples obtained by means of **retrospective collection** from existing sources may not be eligible if the subject’s identity is readily ascertainable to the researchers through direct or coded identifiers or the information is obtained from nonpublic sources such as medical records. If the samples are given to the investigator with any hospital numbers, codes or links that tie the data back to a list of subjects, then there is a mechanism in which the subject can be identified, directly or indirectly and the research does not qualify for exempt review in this category.

Recording identifiers

It is important for the person making the exempt determination to understand the investigator’s plans for recording the data. Temporarily recording a name or other identifiers that allow individual subjects to be identified will exclude this type of research activity from meeting the exempt 4 criteria.

Definition of Human Subject and Coded Private Information/Data or Coded Specimens

Exemption Category 4 is difficult to apply because in some cases the activities do not technically meet the category but still do not require expedited or full review because they do not meet the federal definition of “human subject” (i.e. identity of the subject is not readily ascertainable by the PI).

For example, if the research involves only coded private information/data or coded specimens, OHRP does not consider the research to involve human subjects as defined under the HHS Protection of Human Subjects Regulations (45 CFR Part 46.102(f)) *if* the following conditions are *both* met:

- the private information/data or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; *and*
- the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
 - (a) the key to decipher the code is destroyed before the research begins;
 - (b) the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased;
 - (c) there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased
 - (d) there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

To demonstrate how the determination of whether a research study is human subjects research differs from the determination of whether a human subjects research study is exempt under 45 CFR 46.101(b)(4), consider the following examples, in which an investigator obtains health information of living patients who were treated for arthritis with either Drug A or Drug B. The investigator obtains this information in order to evaluate and compare the treatment outcomes associated with these two drugs:

- (1) An investigator receives only coded information on the treatment outcomes of patients treated for arthritis with Drug A versus Drug B from the patients’ treating physician. The only involvement of the treating physician is to provide coded information to the investigator. The investigator and the treating physician enter into an agreement prohibiting the release of the key to decipher the code to the investigator under any circumstances, until the individuals are deceased. In this example, the investigator is not conducting human subjects research because the investigator cannot readily ascertain the patients’ identity.
- (2) An investigator obtains individually identifiable information on the treatment outcomes of patients treated for arthritis with either Drug A or Drug B by viewing patients’ existing individually identifiable medical records at the clinics where the patients were treated. The investigator records the patients’ treatment outcomes in a coded manner that could permit the identification of the patients. In this example,

the investigator is conducting human subjects research because the investigator is obtaining identifiable private information from patients' (and now subjects') medical records. The study would not be exempt under 45 CFR 46.101(b)(4) since the investigator is recording the information in a coded manner, thus allowing the subjects to be identified indirectly through identifiers linked to the subjects.

- (3) An investigator obtains individually identifiable information on the treatment outcomes of patients treated for arthritis with either Drug A or Drug B by viewing patients' existing individually identifiable medical records at the clinics where the patients were treated. The investigator records only patient age, sex, diagnosis, treatment, and health status at the end of 6 months of treatment so that the investigator cannot link the recorded information back to the patients. In this example, the investigator is conducting human subjects research because the investigator is obtaining identifiable private information from patients' (and now subjects') medical records. However, the study would be exempt under 45 CFR 46.101(b)(4) since the investigator records the information in such a manner that subjects cannot be identified either directly or indirectly through identifiers linked to the subjects.

Category four does not apply to FDA regulated research.

(5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payments for benefits or services under those programs.

This category applies to:

- (i) the projects conducted pursuant to specific federal statutory authority such as programs under the Social Security Act, or other federal statutory public benefit or services programs;
- (ii) procedures for obtaining benefits or services under those programs;
- (iii) possible changes in or alternatives to those programs or procedures; or
- (iv) possible changes in methods or levels of payment for benefits or services under those programs.
- (v) projects for which there is no statutory requirement for IRB review;
- (vi) projects that do not involve significant physical invasions or intrusions upon the privacy interests of participants;
- (vii) authorization or concurrence by funding agencies that exemption from IRB review is acceptable.

This category of research is narrowly defined and only applies to Social Security Act programs and other public benefit programs that are specifically designated by the Department of Health and Human Services or the Secretary of one of the 18 other Federal Departments which have adopted the Common Rule. This criterion is so specific that the University of Kentucky IRB rarely receives applications that fit in this category.

Research and demonstration projects in general (e.g. state funded public service programs) do not fit in this category. Only projects which are conducted under federal statutory authority or the Social Security Act fit under this exemption criterion. OHRP recommends that institutions consult with the investigator's Department of Health &

Human Services (HHS) funding agency before determining that a research project meets research category 5.

This category does not apply to FDA regulated research.

(6) Taste and food quality evaluation and consumer studies, (i) if wholesome food without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

This category addresses two different types of research activity.

1. First, if the taste test involves wholesome food without any additives it is then eligible for exemption. The IRB reviewer must make sure that the food product to be researched is “wholesome” (no additives).

An example of such a research project would be a taste-test conducted on different types of grapefruit to determine consumer preference. The grapefruits are those normally grown in different sections of the country, using normal agricultural practices, and do not involve the addition of food additives or chemicals. The subjects merely indicate which of the grapefruit tasted they prefer.

2. The second item (ii) is more difficult to understand. Research conducted on human subjects who consume plants or animals raised for food products may qualify for exempt review.

The Food and Drug Administration has determined levels of safety for various agricultural chemicals, referred to as GRAS (FDA generally recognized as safe) and GRAE (generally recognized as effective) additives which are fed to animals raised for food production. If these agricultural additives are given to animals at or below the levels found to be safe by FDA, the research can receive exempt review.

An example of such research would be taste-testing pork products where the swine have been fed corn and a chemical additive at a level designated below FDA guidelines that make the animal gain weight more quickly. The objective of the study is to determine whether the addition of the chemical changes the flavor of the pork.

There are also approved levels for environmental contaminants set forth by the Food and Drug Administration, the Environmental Protection Agency (EPA) or the Food Safety and Inspection Service of the U.S. Department of Agriculture (USDA) that may affect the grass or grain consumed by grazing food animals such as chemicals sprayed on a field to combat chickweed. If the research involves taste-testing of food products that come from animals exposed to environmental contaminants and the investigator can show that the use of these contaminants was at or below those approved levels, the research can receive exempt review.

In all of these situations, the investigator should provide some documentation that the alterations, either chemical, environmental or agricultural, have been found to be safe by FDA, USDA, and/or EPA.

However, if there have been food and color additives incorporated into the food product and these additives are used in research with the intent to apply to FDA for marketing that additive, the research would not qualify for exemption. Even if the procedures are preliminary in nature, if the research would eventually lead to FDA approval for marketing the food or color additive, it would not qualify for exempt review. The additives are viewed as investigational by FDA and, therefore, do not meet the exemption criteria.

2008 Guidance from OHRP regarding exemptions and the HIPAA Privacy Rule

The Privacy Rule and the IRB regulations differ with respect on what is considered individually identifiable.

The Privacy Rule is a Federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 (see 45 CFR part 160 and subparts A and E of part 164). The Privacy Rule permits covered entities under the Rule to determine that health information is de-identified even if the health information has been assigned, and retains, a code or other means of record identification, provided that:

- (1) the code is not derived from or related to the information about the individual;
- (2) the code could not be translated to identify the individual; and
- (3) the covered entity under the Privacy Rule does not use or disclose the code for other purposes or disclose the mechanism for re-identification (see HHS guidance entitled, *Institutional Review Boards and the HIPAA Privacy Rule*, page 6, Q and A #3, at http://privacyruleandresearch.nih.gov/pdf/IRB_Factsheet.pdf).

Regarding condition (1) above, in contrast to the Privacy Rule, information that is linked with a code derived from identifying information or related to information about the individual is not considered to be individually identifiable under the HHS regulations for the protection of human subjects at 45 CFR 46.102(f), if the investigators cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimen pertains. Therefore, some coded information, in which the code has been derived from identifying information linked to or related to the individual, would be individually identifiable under the Privacy Rule, but might not be individually identifiable under 45 CFR part 46.

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