

*This Help Sheet is adapted from the Office for Human Research Protections (OHRP) educational video on research use of human biological specimens and other private information.*  
[http://videocast.nih.gov/ram/ohrp\\_kaneshiro.ram](http://videocast.nih.gov/ram/ohrp_kaneshiro.ram).

Three threshold questions are important to consider in addressing whether the regulations for the protection of human subjects would apply to a given activity:

1. Does the activity involve research?
  - a. Sometimes studies that involve the collection or banking of specimens or other data for future unspecified research will raise the question of whether such activities will constitute research under the regulatory definition.
  - b. It is OHRP's view that such activities will often meet the regulatory definition of research since they will constitute systematic investigations that are designed to develop or contribute to generalizable knowledge.
2. Will human subjects be involved in the activity? There are two ways in which an individual becomes a human subject under the regulations.
  - a. If an investigator is intervening or interacting with a living individual for a research purpose to obtain a specimen or other information.
  - b. If an investigator is obtaining individually identifiable private information or specimens. Individually identifiable information means that the identity of the individual to whom the specimen or the data pertain can be readily ascertained or readily associated with the information by the investigator.
3. Is the human subjects research activity exempt? The exemption that most often applies to research involving human biological specimens or data is exemption four.

#### Q & A

**Q:** The definition of human subject references the investigator obtaining data or private information. It does not mention the use of human biological specimens. So why do the regulations apply to the research use of human biological specimens?

**A:** OHRP interprets human biological specimens to be private information. So, if an investigator obtains a specimen from a living individual through a research intervention or interaction, then the research would involve human subjects under the regulations. In addition, if an investigator obtains individually identifiable specimens about living individuals, then the research will also involve human subjects.

Q : Are there instances when an investigator could use specimens or other private information for research purposes without involving human subjects?

A: Yes. If two things are both true, then the research would not involve human subjects. The first is if the research does not involve an investigator either intervening or interacting with a living individual in order to obtain data or a specimen. The second thing would be if the investigator does not obtain individually identifiable private information or a specimen about living individuals.

Example: A research study that would not involve human subjects would be a study that involves the investigator obtaining data that was solely collected for clinical purposes and before the investigator OBTAINS this information, all of the identifiers would be removed from the clinical data before being provided to the investigator. There was no research intervention or interaction to obtain the data, since it was collected solely for clinical purposes and the investigators do not receive information that would allow the researchers to identify the individuals to whom the data pertain.

Q: What if specimens or data are coded? Are they then individually identifiable?

A: Generally, coded information is considered individually identifiable, but there are exceptions to this. Remember, to meet the definition of individually identifiable, the information by which the identity of the individual to whom the information pertains must be either readily ascertainable or associated with the information by the investigator. So, if there are mechanisms that are put into place that would prevent a recipient investigator from being able to readily ascertain the identity of the individuals to whom the data or specimens pertain, even if the information is coded, the investigator would not be considered to have individually identifiable information and human subjects would not be involved in that type of a research activity.

Q: But, if specimens or other private information is coded, wouldn't it be possible to identify the individuals to whom the private information or specimens pertain?

A: Yes, generally a code is retained with the information in order to allow someone to be able to re-identify the individuals from whom the specimens or the information pertain. However, the key, under the regulatory definition of human subjects is whether the investigator will be able to re-identify the individuals. OHRP guidance discusses this in more detail.

<http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm>

Example: Establish an agreement between the provider of the coded specimens and the recipient investigator whereby it is agreed that the recipient investigator will not obtain the key to the code that would enable individuals to be re-identified under any circumstances. At least until the individuals to whom the coded private information or specimens pertain are deceased. These data are not considered individually identifiable because the recipient investigator is not able to readily ascertain the identity of the individuals to whom the data or specimens pertain.

Q: If there is a firewall that prevents the investigator from obtaining or accessing individually identifiable information, then human subjects would not be involved and the regulations would not apply?

A: Yes, provided that there is no research intervention or interaction with a living individual in order to obtain the specimens or data.

Q: Is the person providing the investigator with the coded provide information considered an investigator?

A: It depends on the role of the person providing the coded specimens or data. If the person's role is limited to simply providing the coded specimens or data to investigators, then that person is not an investigator in that research.

Example: In a research repository that involves the collection or that actually maintains a collection of specimens or data for research purposes, and the only role of such a repository in a research study is to provide coded specimens to recipient investigators, but will not have any other role in the conduct of that research, then the repository staff who are providing the specimens and retaining the key would not be considered in that research activity.

Conversely, consider a research repository, however in a particular research study, let say that the repository staff are not only providing the coded specimens or data to recipient investigators and retaining a key, but will also be involved in analyzing any resultant data that's derived from the specimens. If the person/staff providing coded specimens or data also collaborates on other activities related to the conduct of this research, those individuals ARE investigators. Even if there were a so-called firewall established, between the repository staff and the recipient investigator, in that case the research is considered to involve human subjects since at least one or more of the members of the research team would be able to readily ascertain the identity of the individuals to whom the coded specimens or data pertain. If any of the investigators are able to identify the individuals, then the research will involve human subjects.

Q: If a research study involving coded specimens or other private information is determined to involve human subjects, does that mean that all institutions involved in the activity are engaged in human subjects research?

A: Not necessarily, you must examine the specific activities being conducted by all of the institutions involved in a given research activity and keep in mind that only those institutions that are determined to be engaged in human subjects research are required to have a Federal wide assurance (FWA) with our office, and that an IRB designated under that FWA would be required to review and approve any human subjects research to be conducted at that given institution

Example: Consider a study that involves the obtaining of specimens through intervention or interaction with a living individual for research purposes, and so it does qualify as human subjects research generally and would not qualify for an exemption either. There is also another

institution that will be involved only in the analysis of coded specimens and that the recipient institution will be conducting the analysis of the coded specimens and there is an agreement in place that would prohibit those recipient investigators at the other institution from ever having access to the key to the code that would allow for them to re-identify the individuals to whom the specimens pertain. The recipient investigators are not considered engaged in human subjects research.

Q: The considerations for when research involves human subjects seem similar to the considerations for whether an institution is engaged in human subjects research. What is the difference, if any?

A: Yes, the considerations are similar but not identical. The three threshold questions and the order they are asked are important in this distinction and a fourth question is relevant to the engagement question. Note that taking any of these questions out of order can lead to incorrect conclusions. So recall the questions and now add a fourth;

1. Does the activity involve research?
2. Will human subjects be involved in the activity?
3. Is the human subjects research activity exempt?
4. Are the institutions involved considered engaged in the conduct of the human subjects research?

Q: What is the distinction between the use of existing specimens and other private information which does not involved human subjects versus when their use is exempt?

A: First, remember the three threshold questions:

1. Does the activity involve research?
2. Will human subjects be involved in the activity?
3. Is the human subjects research activity exempt?

Only if you have answered affirmatively to questions 1 & 2, and that the activity does indeed involve both research and human subjects, then do you ask the question of exemption. The exemption that is most often applicable to research involving human biological specimens or data is exemption 4. Under exemption 4, the exemption pertains to research that involves existing data, documents or specimens, provided that at least one of two conditions is met, that the information or the specimens be publicly available, or that the information be recorded by the investigators in such a manner that subjects could not be identified either directly or indirectly through links that are retained with the data.

So there are really three factors to focus on when determining when exemption 4 is applicable to a human subjects research study.

1. Are the specimens or data existing at the time the research is proposed for exemption?

2. Are the specimens or data publicly available, meaning available without restrictions? (In most cases, human biological material would not be considered publicly available)
3. If not publicly available, are the data recorded by investigators so subjects cannot be identified, either directly or through identifiers linked to the subjects? If the information is recorded by the investigators in a coded fashion, then exemption 4 would not apply.

Two Examples:

**A study that uses coded information but does not involve human subjects.**

A research study where an investigator is interested in looking at the efficacy of two forms of chemotherapy treatment for a particular type of cancer. As part of this research study the investigator is obtaining data that was collected for clinical purposes and will only be receiving coded data. Also, there is an agreement established between the provider of the coded specimens – the clinicians in this case for the patients – and the recipient investigator, such that the recipient investigator will never have access to the key to the code that would enable the investigator to re-identify the individuals. This study does not involve human subjects because there had not been a research intervention or interaction to obtain the data, given that the data being used in the research study were collected solely for clinical purposes. In addition, because the investigator is not readily able to ascertain the identify to whom the information pertained the information would not be individually identifiable to the recipient investigator, and therefore human subjects would not be involved in the research activity.

**A study that does involve human subjects but meets the requirements of exemption 4.**

A research study where an investigator is interested in looking at the efficacy of two forms of chemotherapy treatment for a particular type of cancer. The investigator will go to the clinic where the patients are treatment an looking at fully identifiable records of these patients to extract the data. In this case, the investigator is recording certain information from those medical records. Let's say they are recording the diagnosis of the patients, treatments received, clinical outcomes associated with the treatments and some limited demographic information such as age or sex of the patient. In this case, the research would involve human subjects because the investigators are obtaining individually identifiable private information because they are seeing the fully identifiable medical records of the patients. However, since the investigators are recording the information in such a way that they're not able to identify the individual subjects, either directly or through identifiers linked to the subjects, then this would be an example of a human subjects research study that would qualify for exemption 4.