

Institutional Review Board Consideration of Chart Reviews, Case Reports, and Observational Studies

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**Introduction: What Constitutes Human-Subjects Research?
Authorized Access to Protected Health Information
Types of Research Review Relative to Observational Studies
Examples of Observational Research
Summary**

Though the need for human-subjects review is readily apparent to investigators when conducting a randomized clinical trial, that same requirement is often less obvious when considering activities such as chart reviews, observational studies, or even case reports. In some cases all that is needed is notification of the institutional review board, which might then exempt the research. In other cases, waiver of consent and Health Insurance Portability and Accountability Act authorization may be granted, whereas in some situations risk to privacy may be considered too great and approval denied. In all cases, including case reviews, quality-improvement projects, and chart reviews, the most cautious approach for the investigator is to discuss regulatory requirements with the institutional review board official to ensure compliance. I will review what constitutes human-subjects research and how investigators may access protected health information, and consider some examples of observational research. Key words: *observational studies, de-identified data, human-subjects research.* [Respir Care 2008;53(10):1350–1353. © 2008 Daedalus Enterprises]

Introduction: What Constitutes Human-Subjects Research?

Although individual institutions may have unique requirements, research undertaken by investigators funded by federal grants is subject to the rules set forward by the

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Department of Health and Human Services in the Code of Federal Regulations.¹ These rules mandate institutional review board (IRB) review of any research with human subjects. Though both “research” and “human subjects” might seem self-explanatory, they are defined in a relatively specific manner. Research is defined as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.” Human subjects are considered “individuals whose physiologic or behavioral characteristics and responses are the object of study in research.” Under federal rules, human subjects are defined as “living individuals about whom an investigator conducting research obtains: (1) data through intervention or interaction with the individual or (2) identifiable private information.” In some states, individuals who have died are still afforded the protections offered human subjects. As a consequence, research that involves autopsy results and death registries may require IRB approval.

Applying these definitions, an investigator or IRB might interpret a wide array of studies as constituting human-

subjects research. For instance, presenting a quality-improvement project at a conference would probably be “contributing to generalizable knowledge.” In contrast, a review of adverse events that occur after a change in a local protocol, if used specifically for altering local behavior, is unlikely to require regulatory approval. Recognize that the distinction here is not whether the data are obtained prospectively or retrospectively, but whether identifiable information is accessed.

What about research that uses non-identifiable data? Even though this would probably not constitute human-subjects research, based on the above definition, most institutions still require IRB review to confirm the investigator’s interpretation. In this case the review process is usually very brief and would result in a certificate of exemption. It is far better for an investigator to pursue this query with the IRB in advance rather than be denied regulatory approval when trying to present or publish the data. More and more journals require proof of such review.

Authorized Access to Protected Health Information

When an IRB considers a study, one of the major issues is compliance with the Health Insurance Portability and Accountability Act (HIPAA).² HIPAA was designed to protect patients’ privacy and ensure their ability to have an accounting (for up to 6 y) of individuals who have accessed their medical records. HIPAA regulations were extrapolated to clinical research and essentially require permission to access a clinical record. Access to protected health information may be granted if there is documentation of informed consent, de-identification of data elements, creation of a limited data set and a data-use agreement, or authorization for waiver of consent and HIPAA authorization. Informed consent and waiver of consent are discussed further in another paper from this symposium.³ Waiver of HIPAA authorization (ie, permission to access protected health information) generally requires proof of several key components:⁴

- The use or disclosure of protected health information involves no more than minimal risk to the privacy, safety, and welfare of the individual.
- The research could not be conducted without the waiver or alteration.
- The research could not practicably be conducted without access to the protected health information.
- There is an adequate plan to protect the identifiers from improper use or disclosure.
- There is an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification

Table 1. Private Health Information Identifiers

Names
Geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code and equivalent geocodes, except for the initial three digits of a zip code if the geographic unit formed by combining all ZIP codes with the same 3 initial digits contains more than 20,000 people
All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death, and all ages over 89
Telephone numbers
Fax numbers
Electronic mail addresses
Social Security numbers
Medical record numbers
Health plan beneficiary numbers
Account numbers
Certificate/license numbers
Vehicle identifiers and serial numbers, including license plate numbers
Device identifiers and serial numbers
Web uniform resource locator (URL)
Biometric identifiers, including finger or voice prints
Full-face photographs or any comparable images
Internet Protocol addresses/numbers
Any other unique identifying number, characteristic, or code

for retaining the identifiers or such retention is otherwise required by law.

- There is adequate written assurance that the protected health information will not be re-used or disclosed to a third party, except as required by law, for authorized oversight of the research, or as permitted by an authorization signed by the research subject.

The other 2 types of access to protected health information include use of de-identified data or a limited data set. Again, this does not mean that the investigator does not need to seek IRB approval if using these type of data. Research that uses data sets such as these usually goes to the IRB for approval, often in an expedited way, so that a waiver of HIPAA authorization can be granted. De-identified data may seem like data that just do not have direct identifiers such as names, medical record numbers, or social security numbers. Though it is true that de-identified data do not contain those elements, much more rigorous criteria must be applied before a data set is considered de-identified. As defined by the HIPAA privacy rule, to be de-identified, 18 identifiers (Table 1) must be removed, and the remaining data cannot be expected to identify a subject.⁵

Note that de-identifying data according to these rules does not allow re-identification of subjects. However, these types of data may be readily available in public databases and allow access to a wealth of stored information, without needing to access individual records. Another way of confirming a truly de-identified data set, in lieu of the removal

Table 2. Elements That Must Be Removed From a Limited Data Set

Names
Postal address information, other than town/city, state, and zip code
Telephone numbers
Fax numbers
Electronic mail addresses
Social security numbers
Medical record numbers
Health plan beneficiary numbers
Account numbers
Certificate/license numbers
Vehicle identifiers and serial numbers, including license plate numbers
Device identifiers and serial numbers
Web uniform resource locators (URLs)
Internet protocol addresses/numbers
Biometric identifiers, including fingerprints and voice prints
Full-face photographs or any comparable images

of all 18 elements noted above, is to show by statistical analysis that the data in the data set cannot realistically identify a subject.

Access to protected health information may be granted by use of a limited data set in conjunction with a data-use agreement. In this situation, slightly more information is allowed in the data set, but there must be a data-use agreement between the provider and the recipient of the limited data set (Table 2), which sets out specific parameters for use of the data and clear acknowledgment that the data will not be used to identify or contact subjects.⁵

Of the above 2 options, de-identifying data is the more common approach and works well for use of large data sets (eg, available after the end of a clinical trial, publicly available data sets, and repositories). It is also a mechanism to keep basic, non-identifiable, information after the end of a study, at which point the investigator has agreed to destroy any links to identifiable data.

Types of Research Review Relative to Observational Studies

Upon receipt of a study for review, IRB committee members will consider the study proposed, risks (physical and to the subject's privacy), and the type of access to protected health information that has been requested. Based on the specifics of the study, the IRB will often assign the study for review to one of 3 categories:

- Exempt.⁶ If deemed "exempt," the investigator must still submit the study for review to allow the IRB to determine this classification. Examples include education research conducted in education settings, surveys or interviews (unless subjects can be identified), and secondary use of existing data (eg, publicly available data sets or de-identified data). These types of studies often require

departmental review but then can be signed off by IRB personnel without full board approval if they meet specific requirements dictated by the institution. This is usually the quickest review process.

- Expedited (minimal-risk) review. This type of study involves minimal physical or privacy risks to the subjects but does not qualify as exempt. These studies may be reviewable by a subcommittee of the IRB, which is usually faster than full board review.
- Full board review. Studies that do not fall into the above 2 categories require review by and presentation to a fully convened IRB. This type of review often takes the longest. Full board review is the standard for intervention studies, but may be required for an observational, data-collection study if the data are sensitive (eg, pose risk to subjects if disclosed).

Each institution may have its own rules for categorizing the types of research, but the above outline provides a general structure for the types of review that might be expected, depending on the type of study proposed. Keep in mind that even exempt research requires approval by the IRB, even if just to say it is exempt. Also realize that the need for IRB review does not necessarily imply the need to obtain consent—a waiver for consent may be part of approval for many studies, especially those that use existing databases. Again, discussion between the investigator and IRB personnel is critical to identify regulatory requirements specific to the study question.

Examples of Observational Research

- For an upcoming conference, you want to present an interesting clinical case of refractory hypoxemia managed with inhaled nitric oxide. Do you need IRB approval?

Case reviews/case reports are not clearly regulated by the same federal mandates described so far. Some IRBs do not consider them under their purview. Agreement among and between investigators and institutional authorities differs greatly. A study in *The Journal of the American Medical Association* surveyed 124 medical schools, 22% of whom considered a case report a form of research and required IRB review.⁷ In addition, some journals require confirmation of regulatory approval prior to printing case reports or reviews. Each institution may also have concerns about patient privacy and risk management if the patient is clearly identifiable based on the disease discussed. Some hospitals are developing their own criteria, independent of IRBs, to regulate such publications. Until further standardized guidelines are available, investigators are advised to confer with their local IRB and institution regarding applicable policy. As an internal check, ask yourself, "How would a patient or family member feel if he/she

recognized him/herself in an article and hadn't been asked for permission?" In such cases, requesting consent from the patient may resolve the question.

- You were a member of a multicenter trial of high-frequency oscillation in the management of adult patients with respiratory failure. The study is now completed, and you're interested in querying the database about the specific impact of this intervention in bariatric patients. As an investigator, you're provided with a de-identified data set for your evaluation. Does this need to go through the IRB?

Though it does not meet the definition of "human-subjects research," because the data have had all 18 identifiers removed, you still are advised to consult with your IRB. Probably all that will be required is submission of a simple exemption request form that outlines the data to be reviewed and how privacy is protected.

- You are curious about the effect of your institution's critical care practices on the duration of mechanical ventilation over the past 10 years, specifically, before and after institution of spontaneous breathing trials and respiratory-therapist-driven protocols. You want to review medical records to describe the population and their outcomes. Will this require full board approval?

It is likely this will qualify for expedited or minimal-risk review. The study entails secondary data analysis of pre-existing records. Though you will be accessing protected health information, it is not feasible to get consent for access to all those charts. With an appropriate plan in place to ensure data security (eg, limit use of direct identifiers, keep data locked, destroy links as soon as possible), it is likely that the investigator will be able to obtain a waiver of consent and HIPAA authorization for review of these records.

- You are interested in looking at the rate of lip ulcers before and after introduction of a new endotracheal tube holder. You suspect that the new device is better for patients but don't know for sure. The mechanism used now is unique, and if benefit is found, you would like to share this with your colleagues. Is this quality-improvement or research?

In reality, this type of study is both: it started out as a local quality-improvement project, but by the time the investigator is ready to present these data, the study probably qualifies as research because it would satisfy the definition of research as a "systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge." This division between quality-improvement and research, like the situation of case reports, is a gray area for regulatory authorities, although many groups are working on better defining this. The general recommendation is for the in-

vestigator to obtain IRB approval prior to the project if there's a clear plan to report the findings. If this isn't recognized until later, then go back to the IRB and request permission to use the data at that time. Such a request will require an explanation of how privacy risks were minimized, how a study like this would be virtually impossible to conduct with prospective consent and in fact was a study of variation in care, and why this information is important. As with all these examples, early, clear communication with the IRB is advised.

Summary

The determination of what constitutes human-subjects research can be rather convoluted. Federal regulations provide some direction, but there are types of studies (eg, quality-improvement projects and case reports) where the requirements are less than clear. In all cases, though, the IRB will evaluate whether the study complied with HIPAA regulations and access to clinical data was authorized. In some cases this may be through direct informed consent, but it could include mechanisms such as de-identification of the data set or development of a limited data set. Given the differences in local regulations and interpretations of at times indistinct federal guidelines, investigators are encouraged to discuss proposed projects with their IRB in advance. The result may be as simple as obtaining an exemption, or it may require a more extensive process. However, such review will enable the investigator to present the data and/or submit the results to journals with the assurance of local regulatory approval. Most importantly, though, this process is intended to advance scientific knowledge while ensuring the privacy patients deserve.

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