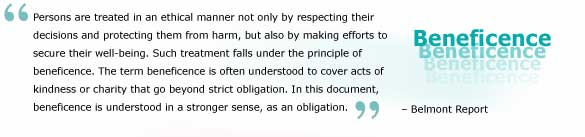
What This Module Covers:

* Risks and benefits
* Privacy and Confidentiality
* Institutional Review Boards (IRBs)
* Data and Safety Monitoring

The Objectives For This Module Are:

* To understand what aspects of research may constitute a benefit to research participants
* To identify possible risks to be considered in evaluating research
* To discuss methods to protect privacy of individuals and confidentiality of data
* To define the role of an IRB to ensure the rights and welfare of human subjects and
* To outline requirements for Data and Safety Monitoring for [***clinical trials***](https://phrp.nihtraining.com/glossary.php#clinical_trial)

Beneficence



Two general rules have been articulated as complementary expressions of beneficent actions:

1. Do no harm
2. Maximize possible benefits and minimize possible harms

[***Investigators***](https://phrp.nihtraining.com/glossary.php#investigator) and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation.

Risk

Risk is the “probability that a certain harm will occur.” [**2**](https://phrp.nihtraining.com/citations.php#cite2)



All research involves some level of risk. We often think of risks in terms of physical harms that may occur as a result of participation in research protocols, but harms may also result from aspects of participation other than from research procedures. For example, harms may result from simply agreeing to be a participant in research, or they may result from disclosure of findings from a research study.

Most risks encountered by participants in research fall into the following categories: [**3**](https://phrp.nihtraining.com/citations.php#cite3)

**A. Physical**

Physical risks may include pain, injury, and impairment of a sense such as touch or sight. These risks may be brief or extended, temporary or permanent, occur during participation in the research or arise after.

**B. Psychological**

Psychological risks can include anxiety, sadness, regret and emotional distress, among others. Psychological risks exist in many different types of research in addition to behavioral studies.

**C. Social**

Social risks exist whenever there is the possibility that participating in research or the revelation of data collected by [***investigators***](https://phrp.nihtraining.com/glossary.php#investigator) in the course of the research, if disclosed to individuals or entities outside of the research, could negatively impact others’ perceptions of the participant. Social risks can range from jeopardizing the individual’s reputation and social standing, to placing the individual at-risk of political or social reprisals.

**D. Legal**

Legal risks include the exposure of activities of a research subject **“that could reasonably place the subjects at risk of criminal or civil liability.”** [**4**](https://phrp.nihtraining.com/citations.php#cite4)

**E. Economic**

Economic risks may exist if knowledge of one’s participation in research, for example, could make it difficult for a research participant to retain a job or to find a job, or if insurance premiums increase or loss of insurance is a result of the disclosure of research data.

## Minimal Risk

Recall that the principle of beneficence involves maximizing possible benefits and minimizing possible harms to research participants. All research involves some degree of risk; however, some research is considered to be of [***minimal risk***](https://phrp.nihtraining.com/glossary.php#minimal_risk).



Minimal risk is defined in the Common Rule to be “that 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(i)**](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.102))

Types of Risk

Because research involves risks, [***investigators***](https://phrp.nihtraining.com/glossary.php#investigator), Institutional Review Boards (IRBs), and other members of the research team must take responsibility for protecting participants against the risks of participating in research. Protections vary according to the kind of risk:

**A. Physical**

In many situations, physical risks in research can be minimized by carefully and skillfully following protocols, by having trained individuals conduct research procedures, through careful monitoring of research participants’ health status, by recruiting appropriate populations, and by providing clinical care when needed.

**B. Psychological**

Possible ways to protect against psychological risks include reminding participants of their right to withdraw from research or limit their participation if they become uncomfortable, providing counseling or psychological support for participants who experience distress, or thoroughly debriefing research participants after research sessions are completed.

**C. Social**

Often, minimizing social risks to participants involves protecting confidential data, including not only the data collected, but the fact of participation in the research project itself.

**D. Legal**

Protections against legal risks often involve protecting the confidentiality of research data. For studies conducted in the United States, investigators can apply for [**Certificates of Confidentiality**](http://grants2.nih.gov/grants/policy/coc/), which are intended to prevent investigators from being forced to disclose data that can be linked to identifiable research participants in legal proceedings.

**E. Economic**

Protecting confidentiality of data is one method for protecting against economic risks, such as those to employability and insurability. Investigators may elect to keep research data separate from medical records in order to prevent employers and insurance companies from obtaining information that could put the participants at risk.

Minimal Risk

Recall that the principle of beneficence involves maximizing possible benefits and minimizing possible harms to research participants. All research involves some degree of risk; however, some research is considered to be of [***minimal risk***](https://phrp.nihtraining.com/glossary.php#minimal_risk).



Minimal risk is defined in the Common Rule to be “that 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(i)**](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.102))

## Designing Research: Anticipated Benefits Greater than Potential Harms



In general, the goal of research is to benefit society by contributing to generalizable knowledge about diseases, disorders, public health concerns, etc. Participation in research may:

* Benefit individual participants or communities
* Neither benefit nor harm individual participants or communities
* Pose risks to individual participants

The HHS regulations apply specifically to individual participants in research and require that:

* Risks are minimized
* Unavoidable risks are justified as necessary for sound scientific design
* Research studies are anticipated to make progress toward important, generalizable knowledge

## Regulatory Requirement for Explaining Benefits and Risks

After minimizing risks to the extent possible, the HHS regulation requires that [***investigators***](https://phrp.nihtraining.com/glossary.php#investigator) consider:

1. **Protections against risks**: Where appropriate, investigators must describe procedures for minimizing potential risks, including risks to confidentiality, plans for ensuring any necessary medical or professional intervention, plans for data and safety monitoring for [***clinical trials***](https://phrp.nihtraining.com/glossary.php#clinical_trial), etc.
2. **Potential benefits to individual participants**: The proposed research has a favorable ratio of potential benefit to risk. This balancing act is often called a **risk-benefit analysis**
3. **Importance of the knowledge to be gained**: Investigators reasonably anticipate that the research will contribute to generalizable knowledge. This generalizable knowledge is considered a benefit to others, and risks to research participants must be reasonable in relation to the importance of the knowledge that reasonably may be expected to result

## Compensation for Research Participation

Some types of research involve a significant commitment from research participants in terms of time or effort, and [***investigators***](https://phrp.nihtraining.com/glossary.php#investigator) may wish to provide [***compensation***](https://phrp.nihtraining.com/glossary.php#compensation).



Institutions should consider establishing standards for fair and appropriate compensation.

During the [***informed consent***](https://phrp.nihtraining.com/glossary.php#informed_consent) process, investigators should explain to potential research participants:

1. If there will be compensation for their participation in the research
2. Appropriate expectations for receiving full, partial, or no compensation if research participants complete the study or withdraw prior to its completion
3. That compensation is meant to reimburse research participants for their time, research-related inconveniences and/or research-related discomforts

Compensation **is not** a benefit of the research.

## Avoiding Undue Inducement



While the use of **inducements** to participate in research is considered appropriate under many circumstances, sometimes inducements can be unduly influential and inappropriate. These are referred to as **undue inducements**. As discussed in the**Respect for Persons**section, the level and kind of [***compensation***](https://phrp.nihtraining.com/glossary.php#compensation) must take into consideration the vulnerabilities of the research population to minimize the possibility of undue inducement.

“Undue inducements are troublesome because:

1. offers that are too attractive may blind prospective subjects to the risks or impair their ability to exercise proper judgment; and
2. they may prompt subjects to lie or conceal information that, if known, would disqualify them from enrolling — or continuing — as participants in a research project.” [**5**](https://phrp.nihtraining.com/citations.php#cite5)

Careful consideration of compensation is not only critical for beneficence, but may be critical for sound research. Considerations should include, but are not limited to, issues like participants’ “medical, employment, and educational status, and their financial, emotional, and community resources.” [**5**](https://phrp.nihtraining.com/citations.php#cite5)

Avoiding the Therapeutic Misconception



Some research studies include examinations, diagnostic tests, and/or interactions with healthcare providers in addition to experimental interventions. These aspects of a research protocol may benefit participants by helping them to better understand a disease or condition, and may help in the participants’ medical decision-making. While it is often appropriate to include treatment procedures in the conduct of research studies, there is a risk that research participants may misunderstand the benefits of research if they think that potential benefits of participation in research are certain. This is called the [***therapeutic misconception***](https://phrp.nihtraining.com/glossary.php#therapeutic_misconception). Therapeutic misconception is the tendency for research participants to:

“… downplay or ignore the risks posed to their own well-being by participation … [due to] the participants’ deeply held and nearly unshakeable conviction that every aspect of their participation in research has been designed for their own individual benefit.” [**6**](https://phrp.nihtraining.com/citations.php#cite6)

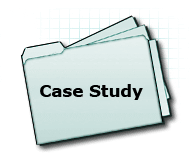
[***Investigators***](https://phrp.nihtraining.com/glossary.php#investigator) should discuss the risks and benefits of research as part of the [***informed consent***](https://phrp.nihtraining.com/glossary.php#informed_consent) process in order to minimize the possibility of therapeutic misconception.

## Assessing Risks and Potential Benefits

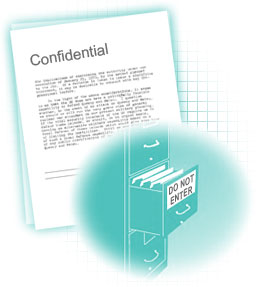


Assessing risks and potential benefits is inexact, but [***investigators***](https://phrp.nihtraining.com/glossary.php#investigator) need to be able to explain to the funding agency, the IRB and the potential research participants how and why the potential benefits of research outweigh the risks of participating in a particular study.

The principle of beneficence requires that investigators consider a number of factors including:

* [***Equipoise***](https://phrp.nihtraining.com/glossary.php#equipoise)
* Protecting the privacy of research participants and the confidentiality of research data
* Establishing oversight mechanisms to protect the rights and welfare of research participants and to determine the significance of the data
* Equipoise and Importance of Knowledge to be Gained
* A state of “[***equipoise***](https://phrp.nihtraining.com/glossary.php#equipoise)” is required for conducting research that may pose risks to research participants.
* 
* For a [***clinical trial***](https://phrp.nihtraining.com/glossary.php#clinical_trial) to be in equipoise, [***investigators***](https://phrp.nihtraining.com/glossary.php#investigator) must not know that one arm of a clinical trial provides greater efficacy over another, or there must be genuine uncertainty among professionals about whether one treatment is superior than another. [**7**](https://phrp.nihtraining.com/citations.php#cite7)
* Equipoise is essential for obtaining generalizable knowledge. If a clear and agreed-upon answer exists, asking research participants to assume the risks of research that will provide the same information is not acceptable; no new knowledge will be gained from the study.
* Case Study: Equipoise in Research Involving Autistic Children
* 
* There are two standard treatments for autistic [***children***](https://phrp.nihtraining.com/glossary.php#children) who display a specific set of characteristics. One treatment is a cognitive behavioral intervention, and the other is a dietary and biomedical intervention. Both treatments have equally strong clinical evidence supporting their efficacy. A researcher proposes a comparison of the two interventions to determine which is preferable. The children will be randomized to one of two groups: half of the children will receive the cognitive behavioral intervention and the other half of the children will receive the dietary and biomedical intervention.
* **Is this study in equipoise?**
* Text: What Do You Think?
* **Yes, this study is in equipoise.**
* **Correct!**
* This study is in equipoise because there is insufficient data to persuade investigators or physicians that one approach is preferable to the other for a child displaying the specific characteristics.
* **No, this study is NOT in equipoise.**
* **The correct answer is Yes.**
* This study is in equipoise because there is insufficient data to persuade investigators or physicians that one approach is preferable to the other for a child displaying the specific characteristics.

## Privacy and Confidentiality



[***Investigators***](https://phrp.nihtraining.com/glossary.php#investigator) are responsible for

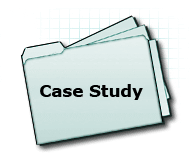
* Protecting privacy of individuals
* Confidentiality of data

**Privacy** means being “free from unsanctioned intrusion.” [**8**](https://phrp.nihtraining.com/citations.php#cite8)

**Confidentiality** means holding secret all information relating to an individual, unless the individual gives consent permitting disclosure. [**9**](https://phrp.nihtraining.com/citations.php#cite9)

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Case Study: Confidentiality in Clinical Research



After the conclusion of a [***clinical trial***](https://phrp.nihtraining.com/glossary.php#clinical_trial) in a small rural community, an [***investigator***](https://phrp.nihtraining.com/glossary.php#investigator) is anxious to publish findings. Understanding the NIH policies encouraging the reporting of demographic differences in intervention effect, and concerned about protecting the confidentiality of research participants, the investigator publishes only general demographic data such as sex, age, state, and county.

**Is this an appropriate and acceptable way to protect the confidentiality of research participants?**

Text: What Do You Think?

**Yes, this is an appropriate and acceptable way to protect the confidentiality of research participants.**

**The correct answer is No.**

Publishing demographic information is only acceptable in situations where the population is large enough, or the disease/condition is common enough that research participants cannot be identified using the demographic data provided. This study was carried out in a small community where it might be easy to identify participants.

For example, these protections were not sufficient after a hantavirus outbreak on an Indian Reservation in the United States. The information published made the identity of one of the individuals who died obvious to the local tribal leaders. In this case the published report not only compromised the identity of the research participant, it also violated the cultural taboo about not speaking of the recently deceased.

**No, this is NOT an appropriate and acceptable way to protect the confidentiality of research participants.**

**Correct!**

Publishing demographic information is not acceptable in situations where the population is small or the disease/condition is rare because it is possible for research participants to be identified using only general demographic data.

For example, these protections were not sufficient after a hantavirus outbreak on an Indian Reservation in the United States. The information published made the identity of one of the individuals who died obvious to the local tribal leaders. In this case the published report not only compromised the identity of the research participant, it also violated the cultural taboo about not speaking of the recently deceased.

## Confidentiality

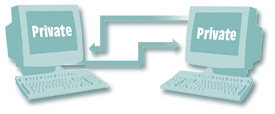
The need for maintaining confidentiality of private information exists in virtually all studies in which data are collected from or about living individuals. In most research, maintaining confidentiality is a matter of following some established practices, for example:

* Properly disposing of data sheets and other paper records
* Limiting access to identified data; and/or
* Storing research records in locked cabinets or secured databases

It may also be appropriate for [***investigators***](https://phrp.nihtraining.com/glossary.php#investigator) to remove direct identifiers from human specimens and data so that they may be analyzed without risk of accidental disclosure of private information. De-identifying data can be done in several ways, including [***coding***](https://phrp.nihtraining.com/glossary.php#coded_data) and [***anonymizing***](https://phrp.nihtraining.com/glossary.php#anonymed_data).

## Coded Private Information and Human Subjects Research

Research with coded private information or specimens involves human subjects if:

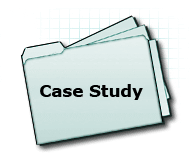


1. The private information or specimens were collected specifically for the currently proposed research project through an interaction or intervention with living individuals; or
2. The [***investigator***](https://phrp.nihtraining.com/glossary.php#investigator)(s) can readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain

Research with coded private information or specimens does not involve human subjects if:

1. The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
2. The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain

## Case Study: Research with Anonymized Data



You are an investigator proposing to use data from a colleague�s database to conduct secondary analyses. You want to examine the behavior and attitudes in male spouses of female business executives. Your colleague will provide coded data for your proposed studies, and you and he enter into an agreement by which he will keep the key to the code and will have no other involvement in the research. Therefore, your colleague is not an [***investigator***](https://phrp.nihtraining.com/glossary.php#investigator) in your research.

**Does this study involve human subjects?**

Text: What Do You Think?

**Yes, this study involves human subjects.**

**The correct answer is No.**

The study does not involve human subjects because both criteria are met:

1. The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
2. The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain

The use of anonymized data means that the investigator cannot identify the individuals to whom the data pertain, and obtaining the data from a colleague with whom the investigator is not collaborating means that the colleague will not be able to link any research results to identifiable individuals.

**No, this study does not involve human subjects.**

**Correct!**

The study does not involve human subjects because both criteria are met:

1. The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
2. The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain

The use of anonymized data means that the investigator cannot identify the individuals to whom the data pertain, and obtaining the data from a colleague with whom the investigator is not collaborating means that the colleague will not be able to link any research results to identifiable individuals.

## Institutional Review Boards

Institutional Review Boards (IRBs) are specialized committees required by HHS regulations that safeguard the rights and welfare of human subjects. IRBs determine “the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice” ([**45 CFR 46.107**](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.107)).

The major roles of IRBs in the oversight of research are:

1. Initial review and approval or disapproval of the proposed research activity
2. Ensuring that the proposed [***informed consent***](https://phrp.nihtraining.com/glossary.php#informed_consent) process meets all of the requirements of [**45 CFR 46.116**](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116)
3. Providing continuing oversight for progress reports and protocols for ongoing research studies
4. IRB Membership
5. 
6. The HHS regulations ([**45 CFR 46.107**](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.107)) require that IRBs have at least 5 members from a variety of backgrounds. The experience, expertise and diversity of the IRB members should allow the IRB to provide a complete and adequate review of the research activities conducted at the institution.
7. Research may involve issues about which IRB members lack specific expertise. In these situations, IRBs should identify and invite individuals with specialized knowledge to assist in the review of applications and protocols where the expertise is required.
8. This issue was raised in the **Respect for Persons** section when discussing the HSS regulations for IRB membership when a study sought to [**enroll a vulnerable population (prisoners) in research**](https://phrp.nihtraining.com/beneficence/prisoners.php). Another example where specific expertise may be needed is when a protocol proposes a study that will recruit participants presenting to a hospital Emergency Department (ED) with acute appendicitis. If the IRB lacks expertise about protections for human subjects in emergency situations, the IRB Chair should ask an expert, such as the head of the ED to advise the IRB on the feasibility of the recruitment strategy.

## Working with the IRB

Although IRBs and [***investigators***](https://phrp.nihtraining.com/glossary.php#investigator) have different roles in research, they have a **shared responsibility** to ensure that research participant protections are appropriate.

As an investigator, you will work most effectively with IRBs if you understand the information that the IRB needs in order to review and approve your proposed research study.

The HHS regulations provide **general criteria** for IRB approval of research, but the specific information that you need to submit may vary among institutions, and may even vary among IRBs at the same institution. You should contact the IRB or Research Administration office at your institution for specific instructions.

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Expedited IRB Review

Protocols may be reviewed either at a meeting of the full IRB or by “expedited review.”

For “certain types of research involving no more than [***minimal risk***](https://phrp.nihtraining.com/glossary.php#minimal_risk) and for minor changes to existing research,” an IRB may choose to use an [**expedited review procedure**](http://www.hhs.gov/ohrp/policy/expedited98.html). The expedited review may be conducted by the IRB chair or by designated experienced IRB member(s) ([**45 CFR 46.110**](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.110)).



[***Investigators***](https://phrp.nihtraining.com/glossary.php#investigator) should understand that **expedited review** is conducted by fewer individuals, but is no less stringent and not necessarily faster than a **full IRB review**. If any individual reviewer who conducts an expedited review is unable to approve a proposed study, the study must be discussed by the full IRB.

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Data and Safety Monitoring



Data and Safety Monitoring Plans describe protections for research participants and data integrity, and oversight for [***clinical trials***](https://phrp.nihtraining.com/glossary.php#clinical_trial) at a level that is commensurate with the risks of participating in the clinical trial. That is, the method and frequency of monitoring is directly related to the possible harms to research participants in the clinical trial.

The HHS regulations require that studies involving human subjects should have a monitoring plan when appropriate ([**45 CFR 46.111**](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.111)).

The NIH requires that all clinical trials supported by NIH have a [**Data and Safety Monitoring (DSM) plan**](http://grants2.nih.gov/grants/policy/hs/faqs_aps_dsm.htm).

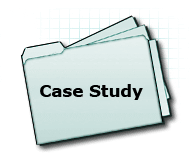
Data and Safety Monitoring Boards



Appropriate protections and oversight can range from oversight by the Principal [***Investigator***](https://phrp.nihtraining.com/glossary.php#investigator) and IRB for a single-site, [***minimal risk***](https://phrp.nihtraining.com/glossary.php#minimal_risk) clinical trial, to oversight by a full Data and Safety Monitoring Board (DSMB) and IRB(s) for a multi-site trial that involves greater than minimal risk.

DSMBs are committees of experts who have no bias with respect to the research and may be permitted to periodically view unblinded data and conduct interim analyses. Principal Investigators must not view unblinded data while their studies are ongoing because they need to maintain objectivity to the extent possible and to ensure integrity of the accruing data.

Case Study: Reducing Exposure to Mercury



An [***investigator***](https://phrp.nihtraining.com/glossary.php#investigator) proposes to work with the community organization of a population where many of the residents are exposed to high levels of mercury through occupational exposure. A previous study indicated that the harms resulting from exposure to a similar heavy metal contaminant could be mitigated through the use of a behavioral intervention. The investigators propose testing the intervention to see if mercury exposure can be reduced in this population. The research design involves randomizing human subjects either to the experimental behavioral intervention in addition to conventional therapy, or to conventional therapy alone. Should the behavioral intervention be determined to be successful, participants who received only conventional therapy will be offered the behavioral intervention after the completion of the study. Research participants will know which intervention they receive because conventional therapy does not include a behavioral component.

**Does this study require a data and safety monitoring plan?**

Text: What Do You Think?

**Yes, a data and safety monitoring plan is required.**

**Correct!**

A data and safety monitoring plan is required because the proposed study is a clinical trial.

Investigators are advised to refer to NIH Institute/Center policies and consult with NIH Program Staff in order to determine the appropriate method for data and safety monitoring.

**No, a data and safety monitoring plan is not required.**

**The correct answer is Yes.**

A data and safety monitoring plan is required because the proposed study is a clinical trial.

Investigators are advised to refer to NIH Institute/Center policies and consult with NIH Program Staff in order to determine the appropriate method for data and safety monitoring.

## Beneficence: Summary

The Belmont principle of beneficence involves maximizing possible benefits and minimizing possible harms to research participants.

Issues covered under Beneficence include:

* Protections against risks
* Definition of [***minimal risk***](https://phrp.nihtraining.com/glossary.php#minimal_risk)
* Methods of weighing risks against anticipated benefits
* Potential benefits for the research participants
* The use of [***compensation***](https://phrp.nihtraining.com/glossary.php#compensation) for participation in research
* [***Equipoise***](https://phrp.nihtraining.com/glossary.php#equipoise) and need for there to be genuine uncertainty about whether one treatment is superior to another
* Privacy & Confidentiality of research participants and research data
* Use of coded private information to protect confidentiality
* Use of an IRB to provide oversight for research involving human subjects
* Situations that allow for an IRB expedited review procedure
* Data and Safety monitoring for [***clinical trials***](https://phrp.nihtraining.com/glossary.php#clinical_trial)