Counting Subjects in Human Subjects Research

When preparing to conduct human subjects research (HSR), researchers should carefully consider the number of subjects needed to carry out the proposed research. Quantitative research and qualitative research employ different approaches to determining how many subjects should be recruited. Use the methods that are generally accepted within your field, which may include power calculations, the total available target population, expected response rates, or feasibility for the researchers.

In general, the higher the level of risk involved in the research, the higher the expectation of rigor in justifying the number of subjects to be recruited. Asking the Human Subjects Committee (HSC) for more subjects than needed may unnecessarily expose subjects to potential research harms. Similarly, asking for too few subjects introduces the same risk, as researchers may be left with insufficient data to draw conclusions from the research; in this case, subjects will have participated for no reason.

Enrolling more subjects than approved by the HSC is a protocol deviation. This is a noncompliance because in the original application the PI certifies that the research will be conducted as described and the PI will request approval from the HSC for changes to the protocol, which includes changes to the sample size. Over-enrolling also raises more general concerns that the PI is not monitoring how the study is being conducted.

How to count subjects

Consider the following categories. (Note: These categories may not apply to every protocol.)

- **Contacted individuals**
  - For studies involving interventions or interactions, these are the total number of people who have been contacted with information about the study to ascertain interest in learning more about or participating in the study (e.g. via phone, mail, email or in person).
  - *The number of contacted individuals does not need to be reported to the HSC, but it can be useful to researchers when evaluating the effectiveness of recruitment strategies.*
- **Screened subjects**
  - For studies involving interventions or interactions, these are the individuals who have given informed consent (if applicable) and participated in screening procedures to determine eligibility.
  - For data- or biospecimen-only research (consent waived or not applicable), these are the total number of unique individuals whose information (e.g., medical record) and/or biospecimens are reviewed to determine which meet the eligibility criteria to be enrolled in a study.
  - *Screened subjects are only counted as enrolled subjects if they go on to participate in some or all of the study procedures, or their data or biospecimens are included in the study analyses.*
- **Screening failures**
  - For all studies, these are the individuals that have only been part of screening procedures and who are determined to be ineligible to take part in the study.
  - *Screening failures are not counted as enrolled subjects.*
- **Enrolled subjects**
  - For studies involving interventions or interactions, these are the individuals who have given informed consent (if applicable) and participated in some or all of the study procedures.
  - For data- or biospecimen-only research (consent waived or not applicable), these are the total number of unique individuals whose information has been used in the study analysis.
  - *The number of enrolled subjects must not exceed the number of subjects approved by the HSC.*
- **Withdrawn subjects**

- For studies involving interventions or interactions, these are the individuals who consented to participate (if applicable) but who withdrew, or were withdrawn by the researcher. This could happen before or after all study procedures are completed.
- For data- or biospecimen-only research (consent waived or not applicable), these are the individuals whose information has been withdrawn from use in the study analysis for some reason.
- *Withdrawn subjects count towards the number of enrolled subjects.*

The numbers in these categories accumulate over the life of the study, not just the current approval period. The number of enrolled subjects, which includes withdrawn subjects, must not exceed the number of subjects approved by the HSC.

Need more subjects?

Researchers may underestimate the number of subjects needed in their initial application. Common reasons for this include:

- Individuals consent, then do not show up to participate or withdraw before completing the study procedures. These people count as enrolled subjects, so the total numbers need to be increased in order to meet the original power calculation for the study.
- The number needed to demonstrate a statistically significant difference between groups was underestimated.
- The researchers find that the actual recruitment pool is much larger than initially believed for their survey. Since the original number of subjects requested were based on an expected response rate of 65% of the total recruitment population, the researchers need to request more subjects to ensure they do not exceed their approved number.

Researchers can submit a modification request to increase the number of subjects approved for a study. Under no circumstances should a researcher increase the number of subjects without HSC approval. If the protocol involves more than minimal risk, the request should be appropriately justified and it will likely have to be reviewed at a full board meeting.

Instructions for submitting a modification in the HARP system are available on our website.

Reporting subject enrollment

It is important to monitor subject enrollment numbers as you'll need to report these in continuing review and annual check-in submissions. You'll be asked to report the following numbers:

- Subject's enrolled at your site
  - This is the number of subjects who meet the definition of "enrolled subject" above, counted only at LBNL. If the study does not involve collaborators or other sites, this number will be the same as the subjects enrolled study wide.
  - This number should not be larger than the number of subjects approved by the HSC.
- Subject's enrolled at your site since last approval
  - This is the number of subjects who meet the definition of "enrolled subject" above, counted only since the last HSC approval was issued or the last annual check-in was submitted.
- Subjects enrolled study wide
  - This is the number of subjects who meet the definition of "enrolled subject" above, counted across all sites participating in the research.
  - For most protocols, this will be the same as the number of subjects enrolled at LBNL.

Examples

Survey Study

An investigator plans to collect data using survey procedures and is granted approval to enroll 1000 participants. A survey is sent to 1000 individuals, and 625 complete and return the survey. After reviewing the responses, the investigators determine that 25 of the responses are missing key answers or do not make sense, and therefore do not contribute to the results. These 25 are withdrawn from the final dataset.

- Total enrollment at this point is 625.
- 25 individuals should be reported as withdrawn by the investigator.
- If the investigator wishes to collect additional data, they may contact more individuals so long as the total number of subjects who complete the survey does not exceed 1000.

Secondary Use of Data Study

An investigator receives existing clinical data to study the mode of action of certain antivirals. The clinical data for 200 individuals is provided with a study code, but the investigator deletes the code and only retains age, sex, viral loads, and drug concentrations. Before beginning the analysis, the investigator screens the dataset and removes 10 subjects with incomplete data.

- Total enrollment at this point is 190.
- If the investigator removes subjects after the analysis has commenced, the total enrollment will still be 190.

Longitudinal Study

As part of a long-term study on how anxiety effects vaccine acceptance, individuals are asked to complete surveys, interviews, and provide measures of blood pressure on an annual basis for five years. The investigator has approval to enroll a total of 700 subjects. One thousand individuals are contacted via telephone and asked if they would be willing to be in the study. Of those, 600 agree and give informed consent and complete all study procedures the first year. In the second year, the investigator is unable to collect data from 50 of these subjects as their contact information is no longer valid and they cannot be located. Ten subjects contact the investigator to say they no longer wish to be involved in the study because it is too time consuming. Data are collected in the second year from the remaining 540 participants.

- Total enrollment at this point is still 600 even though 60 subjects have withdrawn from the study.
- The investigator may enroll an additional 100 individuals.