

Voluntary Withdrawal of Consent

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"Voluntary withdrawal of consent" is the technical term for a study subject deciding to drop out of (i.e., withdraw from) a clinical study.

Clinical study subjects have the right to withdraw from a study at any time and for any reason, or no reason at all. There is no legal requirement for subjects to communicate their withdrawal in writing. In fact, they have the right to be inconsiderate, just stop coming to visits, and let the site deduce that they have withdrawn.

According to the ICH Good Clinical Practice guideline (E6 6.53), study protocols should include the following information:

Subject withdrawal criteria (i.e., terminating investigational product treatment/trial treatment) and procedures specifying:

- a. When and how to withdraw subjects from the trial/investigational product treatment
- b. The type and timing of the data to be collected for withdrawn subjects
- c. Whether and how subjects are to be replaced
- d. The follow-up for subjects withdrawn from investigational product treatment/trial treatment

Protocols should also describe any special requirements related to subject withdrawal, e.g., post-study safety monitoring. Unless it is important for the subject's health, do not require the subject to submit to any testing or data collection as a condition of withdrawal.

Under some circumstances, e.g., pregnancy, a subject might stop receiving the study drug but stay in the study for follow-up visits for safety monitoring and data collection purposes.

Informed Consent Language

Federal regulations and ICH guidelines require consent forms to include a statement about the subject's right to withdraw from a clinical study:

...the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. (21 CFR 50.25(a), 45 CFR 46.116(a)(8))

...the subject may...withdraw from the trial at any time without penalty or loss of benefits to which the subject is otherwise entitled. (ICH 4.8.10(m))

Federal regulations also require consent forms to include information about the consequences of subject withdrawal, "when appropriate":

The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject. (21 CFR 50.25(b)(4)), 45 CFR 46.116(b)(4))

According to the ICH Good Clinical Practice guideline, the site can ask the subject why he or she withdrew, but the subject is not obligated to answer such questions:

Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. (ICH E6 4.3.4)

If withdrawal could have significant consequences or pose any special risks to the subject (or others), disclose these risks in the consent form.¹

The following plain English, consent form statement provides a fairly complete example:

Taking part in this study is your choice. You can leave the study at any time without giving a reason and without penalty or loss of benefits, such as your regular medical care. Also, if you experience a side effect of the study drug, you do not follow our instructions, or for other reasons, we may take you off the study without your consent.

If you decide to leave the study, inform the investigator so we can make the arrangements and discuss your future care. If you stop taking the study drug without gradually reducing the dose, it might damage your lungs. If withdrawal could affect your health in this or another way, we should discuss these affects with you. We may ask you questions about your health and your experience in the study. If you leave the study for any reason, you must return all unused study drug. Also, for your safety, we should continue to monitor your breathing capacity for four weeks. If you leave the study for any reason, you will be paid for the visits and procedures that you completed.

The Final Visit

If possible and necessary, conduct a final visit to conduct the withdrawal discussion, collect unused study drug, perform any appropriate medical tests, and complete the paperwork. Do not collect additional data for the study without making it clear to the subject that these activities are not required (although they might be advantageous to the subject). If there is no final visit, attempt to conduct the withdrawal discussion on the telephone.

In the withdrawal discussion, you may provide factual information to the subject, but not coerce or unduly influence the decision. For example, you may say something like the following:

I respect your decision, but we should discuss some important information about your health. If it's not a burden on you, it would be helpful if we could understand your reasons for leaving the study, so I hope you can answer some questions about your experience in the study. As I said, I accept your decision to leave the study.

However, you may not say things like the following:

You knew what you were getting into when you agreed to complete the study. We were counting on you. We invested a lot of time and money in you, which will now go to waste. I thought you wanted to help others with your disease.

In a constructive manner, explain the consequences to the subject (e.g., possible health effects) of the decision to withdraw from the study and the importance of orderly procedures to wrap up his or her participation. The investigator should make any detrimental consequences clear to the subject, especially if the consequences are significant. Depending on the significance of the consequences, attempts at persuasion might be ethical. Make arrangements for end-of-study activities like return of study drug and drug tapering, and post-study activities like safety monitoring. If appropriate, discuss alternative treatments, and help the subject make arrangements for continuing medical care.

According to ICH's Structure and Content of Clinical Study Reports guideline (E3 10.1):

In appendix 16.2.1 [of a Clinical Study Report], there should also be a listing of all patients discontinued from the study after enrollment, broken down by center and treatment group, giving a patient identifier, the specific reason for discontinuation,

the treatment (drug and dose), cumulative dose (where appropriate), and the duration of treatment before discontinuation. Whether or not the blind for the patient was broken at the time of discontinuation should be noted. It may also be useful to include other information, such as critical demographic data (e.g., age, sex, race), concomitant medication, and the major response variable(s) at termination.

Attempt to obtain information pertinent to the above items, as well as the following information:

- Recent adverse events and other changes in health
- Recent changes in concomitant medications
- The last day of study adherence
- If the subject has not returned the study drug, the amount left
- If the subject has moved, a new address and phone number for follow-up

Without pressing too hard, attempt to determine why the subject withdrew from the study; it might be possible to address the issue or improve his or her attitude toward the experience. You might also learn how to improve subject retention in the future. Ask questions like the following to facilitate a discussion:

- Would it be OK to talk about why you are leaving the study?
- Can you tell us why?
- Did anything surprise you about the study?
- What is your impression of the study drug/device?
- Did you find the study burdensome?
- Did we treat you with respect and consideration?
- What can we do to improve the study experience for others?

A subject might decide to stop participating in the interventional aspects of a study, e.g., taking the study drug, but allow the investigator to continue monitoring the subject's medical condition (with physical examinations, lab tests, CT scans, etc.) and collecting other data. FDA and OHRP guidances discuss this scenario:

If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information as described in the previous bullet, the investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). In accordance with FDA regulations, IRB approval of informed consent documents would be required (21 CFR 50.25, 56.109(b), 312.60, 312.66, 812.100). If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent. However, an investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.²

Continued participation in secondary components of a research study may be particularly important in clinical trials designed to evaluate the safety and effectiveness of specific interventions in the management of diseases or disorders. For this reason, OHRP recommends that when a subject decides to withdraw from a clinical trial, the investigator conducting the clinical trial ask the subject to clarify whether the subject wishes to withdraw from all components of the trial or only from the primary interventional component of the trial. If the latter, research

activities involving other components of the clinical trial, such as follow-up data collection activities, for which the subject previously gave consent, may continue. OHRP also recommends that the investigator explain to the subject who wishes to withdraw the importance of obtaining follow-up safety data about the subject.³

The subject might wish to withdraw entirely from the study but permit the investigator to continue collecting data from medical records and other sources. If so, document the subject's wishes and perhaps obtain a signed consent.

The subject might not be comfortable giving negative feedback to the investigator or study coordinator, in which case, someone else could ask the questions.

If required by the Sponsor or IRB, attempt to obtain a signed withdrawal of consent from the subject. If not, document the subject's withdrawal from the study in a certified letter to the subject.

OHRP guidance recommends reporting subject withdrawals to the IRB, which might be interested in subject welfare and safety implications.³

Subject Data

HIPAA regulations state that data collected prior to the subject's withdrawal from the study is part of the study record and may be used without the subject's consent. Even if the subject objects, FDA and OHRP guidances (although slightly different) make it clear that data collected prior to withdrawal must be retained to comply with regulations and protect the scientific validity of the study. According to OHRP guidance, the use and distribution of biosamples is similar to that of data, except that certain activities related to biosamples may not be conducted after the subject withdraws. For example, if a biopsy has been collected for DNA extraction and analysis, but the DNA extraction and analysis has not been completed prior to withdrawal, it may not be performed thereafter.^{2,3}

The subject might have signed a HIPAA authorization permitting the investigator to transfer the subject's personal health information (PHI) to non-study database, e.g., a disease registry. When the subject withdraws from the study, this permission is automatically terminated for future transfers, although the subject might agree to such transfers in the withdrawal discussion. The non-study database does not need the subject's data to protect the scientific validity of the study, so if a subject wants his or her previously transferred PHI to be removed from the non-study database, that wish probably should be respected. Deidentifying the subject's data might be a practical option.

Once the subject withdraws, the site may not collect further identifiable PHI for the study from the subject or any other source.^{2,3} This prohibition might appear to prevent much of the final-visit discussion described above. However, withdrawal is a process, much of the information requested is not health information, and subjects are not obligated to answer the investigator's questions during that process.

The rules governing the subject's private information are not entirely clear, but the following text can be included in consent forms:

After you leave the study, we will not collect anymore information about you for the study. However, we will still keep, use and disclose any information about you that we obtained while you were in the study.

Lost to Follow-Up

A subject can be considered "lost to follow-up" if he or she misses a visit and study personnel are unable to contact him or her in a timely manner with a minimum of three

documented phone calls. If contact with the subject is not made, follow-up with mail in a process like the following:

1. Mail a certified letter with return receipt requesting contact and expressing concern for the subject's well-being.
2. If the subject does not respond within seven days, mail another certified letter with return receipt stating that the subject's participation in the study has been terminated and detailing the subject's further obligations, such as returning unused study drug.
3. If a signed mailing receipt for the second letter is returned, record the termination date as the date the subject signed it. Otherwise, record the termination date as the date the second letter was mailed.

Regardless of the subject's status on the study, follow up on Serious Adverse Events as usual.

Information about finding lost-to-follow-up subjects is available in the article referenced below.⁴

Involuntary Termination

The subject's participation in a study may be terminated without his or her consent in cases like the following:

- Continued participation in the study could be harmful to the subject's health, e.g., because of a side effect from the study medication.
- The subject becomes pregnant or becomes ill with a condition that prohibits participation.
- After enrollment, it is discovered that the subject does not meet the eligibility criteria, e.g., based on false information provided by the subject.
- The subject needs a medicine or other medical treatment that is not allowed in the study.
- The subject does not take, or is unable to take, the study medication as instructed, does not keep appointments, or otherwise does not adhere to protocol requirements.
- The subject was enrolled by error, e.g., due to misinterpretation of the eligibility criteria or during a poorly managed competitive enrollment period.
- The study is terminated prematurely by the investigator, research institution, sponsor, IRB or FDA.

Some informed consent forms also provide for termination because of "administrative reasons," which is probably a euphemism for "other reasons that might occur but we are unwilling or unable to list them at this time." The consent form language above should suffice.

Before terminating a subject's participation, make every reasonable attempt to address the issue(s), which might or might not be under his or her control. Some flexibility might be required to retain the subject. For example, the subject's work schedule might have changed, necessitating visits at odd hours.

Once a termination decision is made, first attempt to inform the subject in person or by telephone and then by certified mail that his or her participation in the study is being concluded, and explain the reason. If necessary, conduct a final visit like that for voluntary withdrawals. Some subjects might object to termination and might even take legal action, so due care is required.

If a subject dies, obtain a death certificate, coroner's report, or other documentation of the death.

References

1. "The Ethics of Withdrawal from Study Participation," Elisa J. Gordon and Thomas R. Prohaska, *Accountability in Research*, 13:284-309, 2006.
2. "Guidance for Sponsors, Clinical Investigators, and IRBs: Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials," FDA 2008
3. "Guidance on Withdrawal of Subjects from Research: Data Retention and Other Related Issues," OHRP, 2010
4. "How to Find Lost-to-Follow-up Subjects," Kirk Rutherford and Norman M. Goldfarb, *Journal of Clinical Research Best Practices*, September 2005.

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