Interventional Clinical Trial or Registry Study? Writing Protocols that Demonstrate the Difference

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Interventional studies, also called clinical trials, are those in which a drug, device, or procedure is used on research participants as part of a research protocol, and outcome data are collected. Registry studies are observational studies in which the drug, device or procedure being evaluated is prescribed to patients by treating physicians, and outcome data are collected. The critical difference between these study designs is whether the intervention occurs because it is a component of participation in a research protocol, or because a clinical decision was made that the intervention was the appropriate treatment option.

A question that often comes up during Institutional Review Board (IRB) review is whether a research study involves a clinical intervention occurring within the context of the research, or if the research only involves collection of data about an intervention occurring outside of the research. Reviewing the protocol should provide the answer to this question, but often it does not. In this paper, we will address how sponsors/investigators can design research protocols that clearly indicate whether the clinical intervention is occurring within, or outside of the context of the research, and why this distinction is critical in ensuring regulatory compliance.

Why Do These Different Designs Matter?

There may be negative repercussions for subjects when protocols are unclear or a study is improperly described as a registry study, when in fact it is an interventional trial. The risks and benefits of the research may not be identified and analyzed accurately, and consent documents may fail to identify research procedures and research risks. Thus, subjects would not be adequately informed as to what their participation involves (see sidebar).

An example of an interventional trial that may not be identified as such is a study where subjects are assigned to be implanted with an FDA-approved artificial hip system. The research is described as a post-marketing study. The protocol indicates that subjects are eligible to enroll in the study based on their need to receive a hip replacement, and meeting the specific indications for use of this device. These subjects then undergo hip replacement surgery. Data are collected before, during, and after the surgery. Investigators state that subjects will receive the hip replacement regardless of whether they are in the research study. Because of these factors, this could easily be misconstrued as a registry study. However, since the protocol inclusion criteria prescribe use of the device as part of the research, the hip replacement operation using this medical device is a research procedure and the protocol is an interventional trial. Thus the consent form would need to include the hip replacement surgery as a research procedure, as well as the risks of the surgery, and the risks of the artificial hip itself. If the inclusion criteria were modified to indicate that subjects whose surgeons decided to use the device independent of the research would be enrolled, and data collected during, and after implantation, the then protocol would now be a registry study.

When risks associated with the intervention are not identified as risks of the research, the research may improperly be categorized as research involving only minimal risk. In these cases, the protocol may be reviewed by an IRB Chair or an experienced IRB member designated by the IRB Chair (Expedited Review) rather than being IRB-reviewed at a fully convened meeting (Full Board Review), and would therefore be out of compliance with FDA or OHRP regulations.

When protocols are unclear or a study is improperly described as an interventional trial, when in fact it is a registry study, the converse of the above repercussions can occur. Subjects may be told that the research involves risks, benefits and procedures that are not risks, benefits or procedures of the research—they are things that would have occurred as part of their usual medical care. The research may be required to be reviewed through a Full Board Review, rather than by Expedited Review.

Finally, misclassification of interventional trials as registry studies may lead to the research being conducted without fulfilling FDA requirements for an IND or IDE, in cases where an IND or IDE may be required. For example, a study of an approved drug being used outside of its approved dosing range, which does not qualify for an exemption from IND requirements, may be improperly evaluated as being exempt from IND requirements when administration of the drug is a research procedure but the research is misclassified as a registry study.

How Can Research Be Designed to Clearly Differentiate Between Registries and Interventional Trials?

To distinguish between registry studies and interventional trials, the protocol needs to be clear as to what procedures are mandated by the protocol. The protocol title, the purpose, the background and a statement of whether procedures are "standard of care" are usually not sufficient to make this distinction clear. The question that must be explicitly answered is whether the intervention/procedures are mandated by the protocol, or are happening outside of the research.

> Inclusion Criteria

For the protocol to be clear, the inclusion criteria are critical. In a registry study, the inclusion criteria should indicate that the clinical decision to use the drug, device, or

procedure is independent (made outside) of the decision to take part in the research. Interventional trials would not have this criterion, but would instead have medical criteria that would qualify the subject to be eligible to receive the drug, device or procedure.

Comparative examples of inclusion criteria for registries and interventional trials are shown below:

Registry Inclusion Criteria	Interventional Study Inclusion Criteria
A clinical decision has been made to use FlexTech Model 51 knee replacement prior to enrollment in the research.	*Knee pain and limited range of motion that has failed medical treatment with at least two nonsteroidal anti-inflammatory medications and six months of intensive physical therapy.*
A clinical decision has been made to use oral fluoxetine to control severe pruritus prior to enrollment in the research.	*Severe pruritus nonresponsive to topical medication.*
The patient was scheduled to undergo a hysterectomy using laparoscopic technique prior to their decision to participate in the research.	*The patient requires a hysterectomy and meets clinical criteria for a laparoscopic approach.*

> **Comparative Inclusion Criteria for Registry and Interventional Studies**

> Study Procedures

In a registry study, the research procedures are limited to collection of data and do not describe or specify the use of the drug, device, or procedure under study. In an interventional trial, the research procedures describe the use of the drug, device, or procedure under study. Comparative examples of study procedures for registries and interventional trials are shown below:

Registry Procedures	Interventional Study Procedures
Data will be collected before, during, and after implantation of the FlexTech Model 51 knee replacement.	*Subjects will undergo implantation with the FlexTech Model 51 knee replacement.*
Data will be collected regarding the subject's treatment with oral fluoxetine.	*Subjects will be treated with oral fluoxetine 20 mg once a day for six months. Dose may be titrated up to 80 mg per day.*
Data will be collected from the subject's medical records to obtain information regarding the subject's pain before and after the planned hysterectomy.	*Subjects will undergo laparoscopic hysterectomy.*

> **Comparative Procedures for Registry and Interventional Studies**

Conclusion

Differentiating registry studies and interventional trials is required to protect research participants, and is essential to ensure proper regulatory compliance. To distinguish between these two study designs, the inclusion criteria and the procedures involved in the research should clearly indicate what is within the research study and what is outside of the research. In a clearly-designed protocol, this can cut down on IRB review time, prevent questions from the IRB, and ensure proper compliance and subject protection.

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