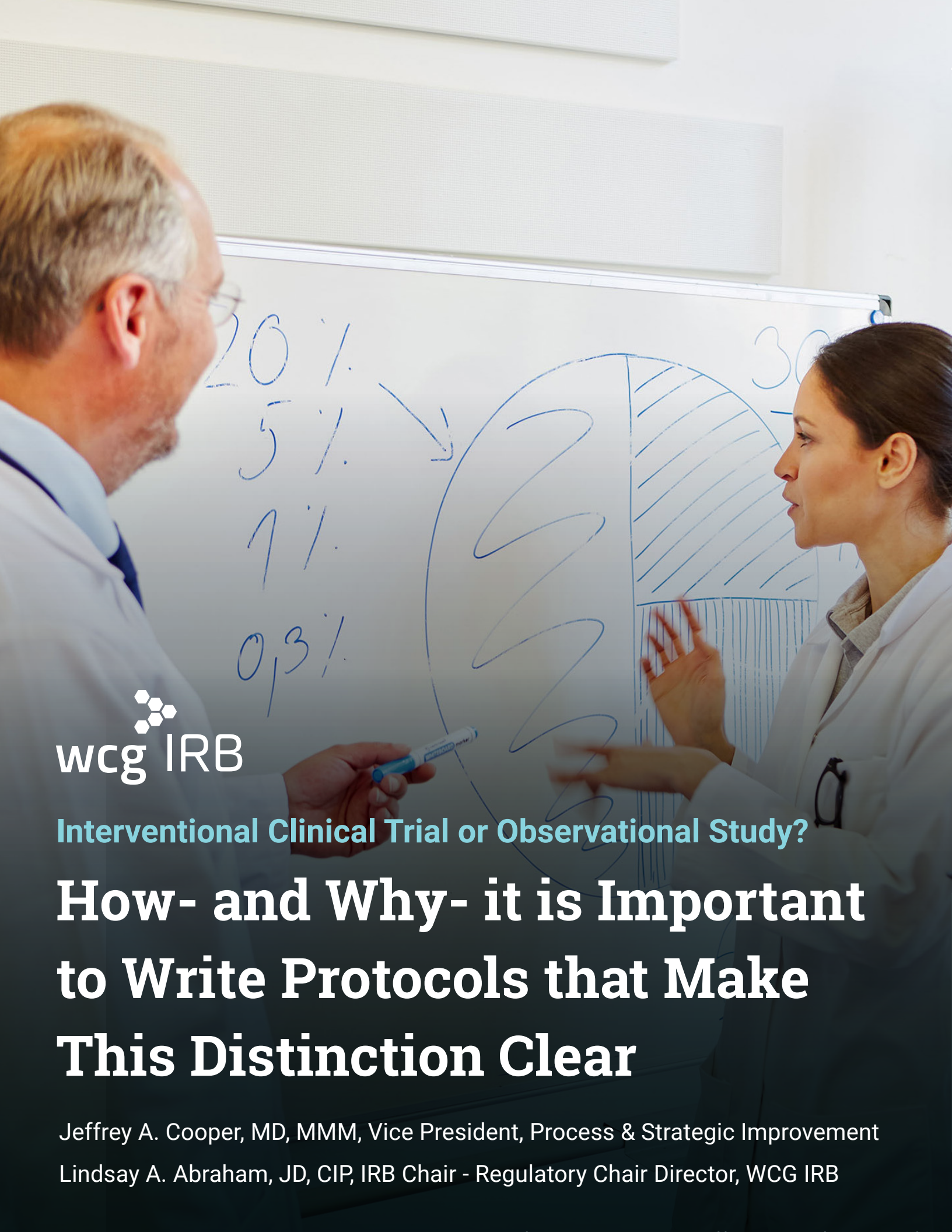

wcg IRB

Interventional Clinical Trial or Observational Study?

How- and Why- it is Important to Write Protocols that Make This Distinction Clear

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Interventional studies, also called clinical trials, are those in which a drug, a device, or a procedure are administered to research participants as part of a research protocol. Studies in which a drug, a device or a procedure are administered to patients by treating physicians independent of the research, and the research only involves the collection of outcome data areobservational clinical studies. Sometimes these types of studies are referred to as data collection studies, or registry studies. 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 outside of the research that the intervention was the appropriate treatment option.

The question of 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, is often not definitively answered by reviewing the protocol. In this paper, we will address how sponsors/investigators can design and write research protocols that clearly indicate whether the clinical intervention is occurring as part of the study, or outside of the context of the research, and why this distinction is critical in ensuring regulatory compliance.

WHY DO THESE DIFFFERENT DESIGNS MATTER?

There are potential adverse impacts to participants when protocols are unclear or a study is improperly described as an observational study, when in fact it is an interventional clinical trial, and also when a protocol is written as if it is a clinical trial when it really an observational study. The correct risks and benefits of the research may not be identified and analyzed, consent documents may fail to identify research procedures and research risks, thus participants would not be adequately informed as to what their participation involves, and the appropriate regulatory standards may not be applied.

An example of an interventional trial, that may not be identified as such, is a study where participants are assigned to be implanted with an FDA-approved hip system. The research is conducted as a post-marketing study. The protocol indicates that participants meet criteria to enroll in the study based on their need to receive a hip implant, and meeting the indications for use of the device. These participants are then implanted with the device. Data are collected before, during, and after implantation.

Investigators state that participants will receive a device regardless of whether they are in the research study. This could easily be misconstrued as an observational study. However, when the protocol inclusion criteria

prescribe use of the device as part of the research and implantation of the device is a research procedure, the protocol is an interventional clinical trial.

Thus the consent form would need to include procedures for implantation of the device, as well as the risks of the implant procedure, and the risks of the device itself. If the inclusion criteria were modified to enroll participants whose surgeons decided to use the device independent of the research, and the procedures only included that data would be collected, before, during, and after implantation, then the protocol would be an observational study.

When Clinical Trials are Treated as Observational Studies:

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 a IRB Chair or and experienced IRB member designated by the IRB Chair (Expedited Review) rather than being reviewed at a fully convened meeting (Full Board Review), and would therefore be out of compliance with FDA/OHRP regulations.

Misclassification of interventional trials as observational 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 may be improperly evaluated as being exempt from IND requirements if the research is misclassified as an observational study when administration of the drug is a research procedure.

When Observational Studies are Treated as Clinical Trials:

When protocols are unclear or a study is improperly described as an interventional trial, when in fact it is an observational study, the converse of the above adverse impacts can occur. Participants may be told that the research involves risks, benefits and procedures that are not risks, benefits or procedures of the research, but rather are things that would have occurred as part of their usual medical care. The research may be required to be IRB-reviewed through a Full Board Review because of the risk of the intervention (which is not actually part of the study), when it could more appropriately be classified as a minimal risk study thatcan be reviewed through an Expedited Review pathway.

OBSERVATIONAL STUDIES VS. INTERVENTIONAL TRIALS

To distinguish between observational studies and interventional trials, the protocol needs to

be clear as to what procedures are mandated by the protocol, and how/when participants are selected to participate. 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. So what does the protocol need to include to make this distinction clear?

1 Inclusion Criteria

For the protocol to be clear, the inclusion criteria are critical. In an observational study, the inclusion criteria should indicate that the clinical decision to administer 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 criterion that would qualify the participant to be eligible to receive the drug, device or procedure.

Comparative examples of inclusion criteria for observational studies and interventional trials are shown in **Figure 1.**

2 Study Procedures

The description of study procedures is Just as important as the inclusion criteria, if not more important. In an observational study, the research procedures do not describe or specify the administration of the drug, device,

Figure 1: Inclusion Criteria

Observational Study Inclusion Criteria	**Interventional Trial 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.

or procedure under study, although they can specify other procedures such as blood tests and radiographic studies. In an interventional trial, the research procedures describe the use of the drug, device, or procedure under study.

Comparative examples of study procedures for observational studies and interventional trials are shown in **Figure 2**.

CONCLUSION:

Differentiating observational studies and interventional trials is important. It is necessary to ensure the protocol is clearly written to distinguish what is occurring as part of the research to adequately protect research participants, and to ensure proper regulatory compliance. To distinguish between these two, 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 participant protection.

Figure 2: Study Procedures

Observational Study Procedures	Interventional Trial Procedures
Data will be collected before, during, and after implantation of the FlexTech Model 51 knee replacement.	Participants will undergo implantation with the FlexTech Model 51 knee replacement.
Data will be collected regarding the participant's treatment with oral fluoxetine.	Participants 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 participant's medical records to obtain information regarding the participant's pain before and after the planned hysterectomy.	Participants will undergo laparoscopic hysterectomy.