When academic research organizations and clinical research organizations disagree: Processes to minimize discrepancies prior to unblinding of randomized trials

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Given the potential impact of a clinical trial on patient care, it is critical that the outcomes of the study be independently verified by multiple parties. To this end, multiple academic research organizations (AROs), contract research organizations (CROs), independent data safety monitoring board (DSMB), and the sponsor often analyze the data independently and in parallel. Discrepancies among these groups analyzing the "same" data may have 2 broad categories of causes, including (1) "objective" differences (eg, programming errors) and 2) "subjective" differences (eg, differences in the interpretation of the statistical analysis plan [SAP]). Whereas objective discrepancies can be resolved by statisticians and programmers based upon objective findings, subjective differences in SAP interpretation require input from multiple stakeholders such as clinical trialists, Clinical Event Committee members, DSMB members, and core laboratories, for instance, to reach consensus regarding the intent and the execution of SAP language. These efforts will facilitate reconciliation of discrepant results prior to unblinding of the trial.

This article describes a clinical trial in which 2 independent AROs involved in the conduct of a randomized trial differed from the CRO and the sponsor in their subjective interpretation of the SAP prior to unblinding. This discrepancy in the interpretation of the SAP was not escalated to involve a broad group of stakeholders other than the statisticians. This led to a difference of one primary efficacy end point event in their respective data sets. As a result, there were discrepant results as to whether the trial met its primary end point. This manuscript outlines a proactive process that can be applied throughout the course of the trial prior to unblinding to reconcile both objective and subjective discrepancies that may be critical to the trial's results.

Background

The Acute Medically Ill VTE Prevention with Extended Duration Betrixaban Study (APEX) trial was a randomized, double-blind, double-dummy, clinical trial that enrolled 7,513 patients who were hospitalized for acute medical illness.[1] The details of the design and the primary results have been reported.[2] Patients were randomized in a 1:1 ratio to receive either subcutaneous enoxaparin for a standard duration of 10 ± 4 days or oral betrixaban for 35 to 42 days. The primary efficacy outcome is the occurrence of any of the following events through to the end of the planned treatment period (visit 3): (1) asymptomatic proximal deep vein thrombosis (DVT) as detected by ultrasound obtained on day 32 to 47 or (2) symptomatic DVT (proximal or distal), nonfatal pulmonary embolism (PE), or venous thromboembolism (VTE)–related death on or before the day of visit 3 or day 42, whichever is earlier. Efficacy time points were defined in the protocol as follows: visit 1 was the date of randomization (day 1 of the study). Visit 2 occurred on the day of discharge or day 14 if the hospitalization was >14 days. Visit 3 occurred between day 35 and no later than day 42. Study drug was discontinued at visit 3. Protocol-mandated compression ultrasound was also performed at or around the time of visit 3. Visit 4 was the final study visit and occurred at least 30 days after visit 3. All symptomatic events were adjudicated by an independent committee. The occurrence of an asymptomatic event was adjudicated by an independent, blinded, core laboratory review of the compression ultrasound.

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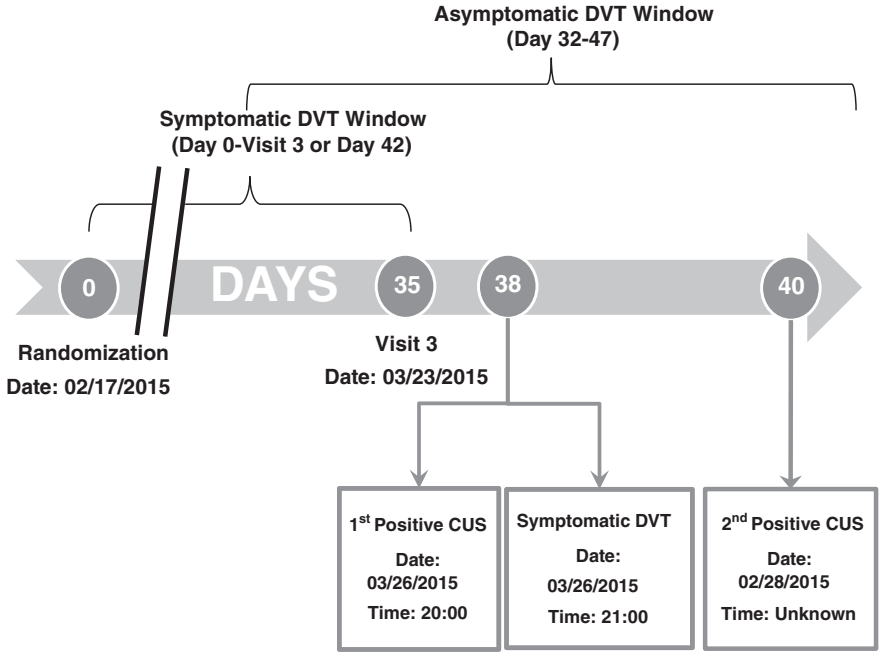
Figure 1



Sequence of events surrounding patient X.

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Language in the SAP

With respect to the inclusion or exclusion of any event for consideration as an end point, the SAP stated the following:

"Symptomatic events for the primary analysis must occur on or before day 42 or the day of visit 3, if visit 3 occurs before day 42. Such events must meet both criteria for patients who have a visit 3: on or before day 42, and on or before the day of visit 3. Supportive analyses may use different day ranges. An asymptomatic event detected the same day as onset of a symptomatic DVT, or within two days after onset of a symptomatic DVT, will not be considered a separate event. It will be concluded that the two events detected the same physical issue, and is likely to happen because the compression ultrasound (CUS) that is used to confirm diagnosis of a symptomatic DVT might also be sent to the ultrasound central laboratory for adjudication. If an asymptomatic event is detected on the same day as, or within two days after, onset of a symptomatic DVT, only the symptomatic DVT will be included in analyses as an event."

Patient X

One patient, referred to hereafter as *patient X*, experienced a sequence of events that led to different interpretations as to whether patient X sustained an event. Figure 1 summarizes the sequence of events that patient X experienced in the study.

Patient X was randomized in February 2015, dosed according to the study protocol, and completed visit 3 on day 35, as planned. The patient reported no symptoms at the time of visit 3. On day 38, at approximately 8:00 PM, the patient underwent a protocol-mandated ultrasound that was positively adjudicated by the independent ultrasound core laboratory as showing venous thrombosis. On day 38, at approximately 9:00 PM, after the positive ultrasound result, patient X reported symptoms that were adjudicated independently by the Clinical Event Committee as a symptomatic VTE event. The patient had a repeat ultrasound on day 40, but the time of this ultrasound is not known. This second ultrasound was positively adjudicated by the central core laboratory as, again, showing venous thrombosis.

Interpretation of whether patient X sustained an event or not

There were discrepancies between the CRO and 2 independent AROs (ARO 1 and ARO 2) as to whether the events sustained by patient X should be included in the