

The importance of an independent oversight committee to preserve treatment fidelity, ensure protocol compliance, and adjudicate safety endpoints in the ATACH II trial

NA McBee¹, DF Hanley^{1,*}, CS Kase¹, K Lane¹, and JR Carhuapoma¹

¹Johns Hopkins University, 1550 Orleans Street, 3M 50 South, Baltimore, MD 21231, USA

Abstract

In response to growing trends and accepted U.S. Food and Drug Administration (FDA) guidance, the ATACH II trial leadership developed the independent oversight committee (IOC) as a mechanism to adjudicate the trial safety endpoints and to evaluate treatment fidelity and protocol compliance. To accomplish these tasks, the IOC reviews the first three subjects enrolled at each study center and all serious adverse events that occur across all study centers. The IOC makes recommendations to the steering committee regarding the aggregation of, or trend in, adverse events at particular sites and discusses homogeneity, or lack thereof, in the principles and intensity of the overall care. Based on the IOC findings, the steering committee will contact individual sites, as needed, to discuss potential remedial measures.

Keywords

ATACH II; endpoint adjudication; treatment fidelity; quality assurance

Introduction

The growing trend in clinical trial research is to incorporate the use of an endpoint adjudication committee into the quality assurance process. The ATACH II trial leadership expanded on this trend by developing the independent oversight committee (IOC) as a mechanism to adjudicate the trial safety endpoints but also to evaluate treatment fidelity and protocol compliance. To accomplish this task, the members of the adjudication committee are independent from the sponsors and the steering committee of the study [1]. Treatment fidelity consists of two general components: (a) treatment integrity, the degree to which a treatment is implemented as intended and (b) treatment differentiation, the degree to which two or more study arms differ along critical dimensions [2]. While the statistical center will eventually determine treatment differentiation, the IOC actively preserves treatment integrity by reviewing the first three subjects enrolled into the ATACH II trial at each study center. Review of protocol compliance in these first three subjects serves to protect treatment fidelity with surveillance of protocol deviations and early detection of sys-

tematic errors within each study center. Performing this review at each study center ensures that treatments are operationalized across sites and reduces the possibility of site by treatment interactions [2]. By monitoring protocol adherence at the beginning of study implementation at each study center and over the course of the study as needed, the IOC assists the ATACH II trial leadership to prevent drift from the protocol, which ensures treatment fidelity.

In addition to preserving treatment fidelity through protocol compliance, the IOC also serves as the endpoint adjudication committee for the trial. The US Food and Drug Administration (FDA) Center for Drug Evaluation and Research defines endpoint adjudication as a process of interpretation of clinical source data to reach a qualitative or quantitative conclusion about what the data show [3]. The FDA manual of policies and procedures acknowledges that many types of clinical source data require minimal or no interpretation after collection, but other clinical source data types require detailed interpre-

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*Correspondence to: DF Hanley, Email: dhanley@jhmi.edu

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tation of expert clinicians to assign endpoint values (i.e., endpoint adjudication) [3]. The differences between investigator reported and central, independent adjudication of safety events have been documented in studies including the TRIM study, the PERT trial of the Women's Health Initiative, the PURSUIT study, and the MODE Selection trial, and in some instances the reported level of disagreement was as high as 10% [4,5]. The adjudication process ensures the best overall data by confirming or correcting the investigator reported events by applying global knowledge from personal clinical experience combined with overall knowledge of the safety profile of the entire trial cohort. The use of the IOC as an endpoint adjudication committee ensures compelling primary endpoints whose use will not be debated after the fact. This important safeguard is achieved by a budgetary investment in the IOC activities that is generally <1% of the total cost of the study [6].

Methods to be applied for IOC activities in the ATACH II trial

After a study subject is randomized into the ATACH II trial, clinical information is data entered by the site coordinator into the WebDCU™ system (remote data entry system). A subject profile report is then created in the WebDCU™ system using these data to summarize subject demographic data, medical history, National Institutes of Health Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS) scores at baseline and at 24 h, intervention data points (high- and low-systolic blood pressure, heart rate, infusion titration, other blood pressure lowering agents, intracranial pressure (ICP) [if applicable]) over the first 24 h, concomitant medications and their doses, procedures performed, and safety event data.

Treatment fidelity and protocol compliance review

The IOC monitors the adequacy of adherence to the protocol and the principles and intensity of overall care at all sites by reviewing the subject profile report for the first three patients recruited at each site. The IOC receives email notification of each randomization (Figure 1). This prompts the IOC program manager to request the de-identified progress notes from the medical chart to allow review of the first 7 days of the hospital stay. The IOC program manager prepares reports for review by graphing the intervention data points to show the systolic blood pressure trends over the first 2 h and over the 2–24-h period. The graphs also show the corresponding nicardipine titrations to help determine intervention-associated hypotension or hypertension. These

graphs, along with the subject profile report and the medical chart progress notes, are circulated to the IOC members for review. The IOC members review the materials and determine the following: (1) was the titration protocol properly administered in the 0–2 h period and the 2–24 h period? (2) was the systolic blood pressure responsive to the treatment regimen in the 0–2 h period and the 2–24 h period? (3) were there any instances of hypotension or other concerns during the intervention? (4) were there any concerns with standard medical management? (5) did blood pressure management achieve control after the 24 h study period? and (6) were there new serious adverse events (SAEs) identified by the reviewer and not reported by the site principal investigator? In addition, if applicable, the IOC also determines: (1) were neurological evaluations completed timely and appropriately performed? (2) was airway managed properly? (3) was ventilator managed properly? (4) was neurological deterioration appropriately followed? (5) was cardiac monitoring timely and appropriately performed? and (6) was ICP monitoring timely and appropriately performed. Based on the IOC review of these parameters, a summary statement is provided as feedback to the coordinating center (CC), the data management center (DMC), and the enrolling center. The statement summarizes if the protocol goals were achieved and if the goals were achieved within the 24 h time frame after randomization. The summary statement also includes a list of any treatment complications that were noted, if any changes to the protocol or consent form are recommended, and if the enrolling center requires remediation or re-training. The IOC reports to the steering committee about any concerns regarding the aggregate data at particular sites related to the principles and intensity of the overall care.

SAE adjudication

The IOC program manager is notified by email using an automated system triggered when a SAE is entered into the WebDCU™ system (see Figure 1). All SAEs are reported to the IOC. The safety outcome of interest for the analysis at the end of the trial is the proportion of subjects who experienced any treatment-related SAEs during the first 72 h from randomization.

The IOC adjudicates the relationship of the SAE to both the study intervention and the principles and intensity of overall care. The IOC makes recommendations to the steering committee regarding the aggregation of, or trend in, adverse events at particular sites and discusses homogeneity, or the lack thereof, in the principles and intensity of the overall care.

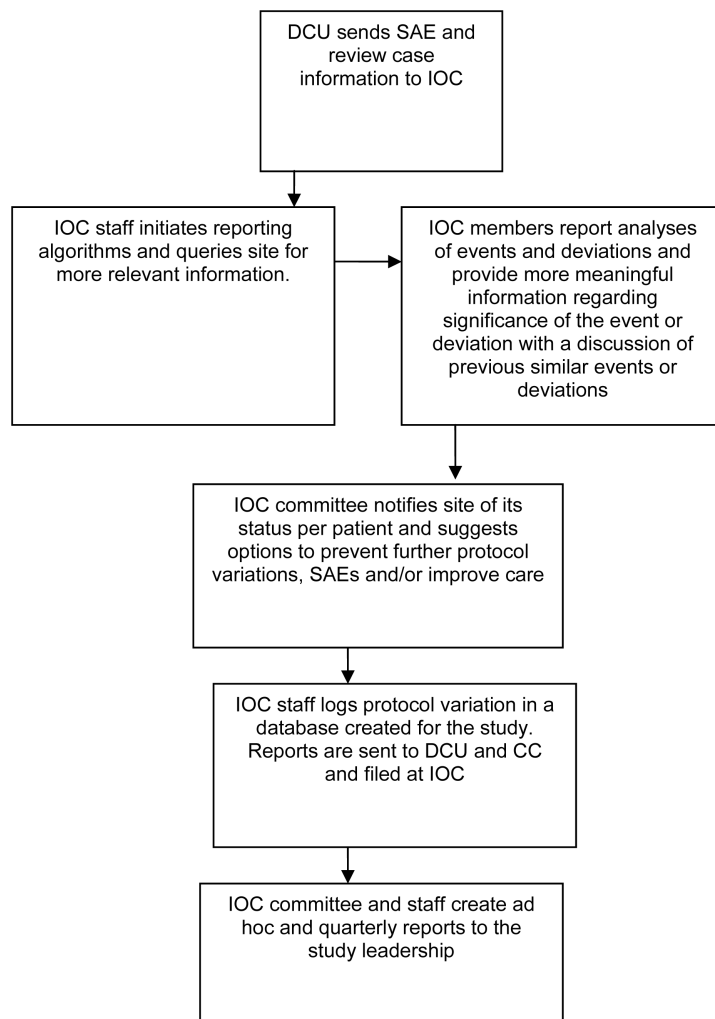


Figure 1. Data flow of the IOC review processes.

Based on the IOC findings, the steering committee will contact individual sites, as needed, to discuss potential remedial measures.

Conclusions

The ATACH II trial leadership recognized the importance of independent adjudication of treatment fidelity and safety endpoints, and incorporated the IOC early in the study implementation process. IOC review of the first three subjects at each enrolling center assists the ATACH II leadership in preventing protocol drift and ensures treatment fidelity. IOC adjudication of all SAEs in the trial ensures compelling primary endpoints whose use will not be debated after the fact.

List of abbreviations

IOC, Independent Oversight Committee; ATACH II, Antihypertensive Treatment of Acute Cerebral Hemorrhage; FDA, Food and Drug Administration; WebDCU, Web Data Collection Unit; ICP, Intracranial pressure; SAEs, Serious adverse events.

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