

CLINICAL ADJUDICATION COMMITTEES: BEST PRACTICES FOR USE IN A RANGE OF STUDY DESIGNS


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OBJECTIVES

By the end of this discussion attendees will be able to

- 1: Explain when adjudication committees are *necessary* versus when they are not necessary, but *useful*
 2. Describe different adjudication committee models and be able to choose between models depending on study needs and resources
 3. Have an understanding of how to implement a clinical adjudication committee into their own studies
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WHAT IS A CLINICAL ADJUDICATION COMMITTEE?

A clinical adjudication committee is typically* made up of 3 or more blinded, unbiased experts, who perform a review of suspected clinical endpoints and/or adverse events.

The goal of a CAC is to standardize the review of clinically relevant endpoints and reduce the bias and variability from investigators involved in the study

You may also hear CACs called endpoint adjudication committees or clinical endpoint committees


WHEN IS A CAC NECESSARY?

1. Anytime the sponsor, funding agency, or FDA requires it

WHEN IS A CAC NOT NECESSARY BUT USEFUL?

1. When the study endpoint(s) are subjective (dementia, anxiety and depression)
2. The study is being conducted in multiple geographies, and therefore clinical practices may vary
3. In studies where endpoints or efficacy and safety outcomes are not easily defined and/or have multiple components (i.e the endpoint cardiovascular disease is made up of multiple components: CV death, MI, and/or stroke) (Pneumonia may be diagnosed biologically, clinically, by radiograph and/or a combination of the 3)

WHEN A CAC IS NOT WORTH IT

1. There is no budget for it
 2. There is no time for it
 3. The endpoint is objective (ex: death, pregnancy, QoL survey score, alcohol/illicit substance use survey score etc.)
 4. It is a time to event study of an objective or easy to define event (ex: microbiologic culture conversion in tuberculosis)
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Summary: When designing a study and deciding whether to use a CAC, the PI and coordinator should determine 1. If it is required by the funding agency and/or the FDA for drug /device trials 2. If it's not required, does it make sense for the type of study and the outcome(s) of interest 3. Is there the time/budget for it?

So..

THE FDA TOLD YOU A CAC IS REQUIRED

OR IT WAS DECIDED THAT A CAC FITS WITH
THE STUDY DESIGN/OUTCOMES AND
WOULD INCREASE THE INTEGRITY AND
RIGOR OF THE STUDY

... Now what



ADJUDICATION MODEL OPTIONS

Internal Adjudication
Committee

Experts from the same
institution

Benefits: if reasonable/ethical for the study, can access the EMR directly, may be geographically closer to one another: helps with training, communication for discrepant cases, troubleshooting, payment etc.

Potential draw backs: Can access the EMR: has access to all patient data, may bias event/time specific endpoints. Although not an investigator on the study, institutional/personal relationships may cause bias

External Adjudication
Committee

Experts from an outside institution
(a CRO, another academic
center, etc..)

Benefits: If *truly* external to the institution and investigators, can reduce risk of bias

Potential draw backs: Can be expensive. If geographically scattered makes training/communication/troubleshooting more difficult. Have to implement a system for patient case review outside of the EMR

ADJUDICATION MODEL OPTIONS: SCALED DOWN

There are scenarios where a full adjudication committee may not fit the study's budget/timeframe, but it would still be useful to have an external reviewer. The most common scenario for this is when there are relevant endpoints that the investigators are not experts in (ex: radiographic endpoints for non-radiologists). Studies tend to employ an internal physician in this scenario since budget is often a driving factor.

We will focus on implementing a CAC with at least 3 reviewers, but the steps can be adjusted for one reviewer. Do note that the ability to discuss case discrepancies is lost under this option.

OBJECTIVES

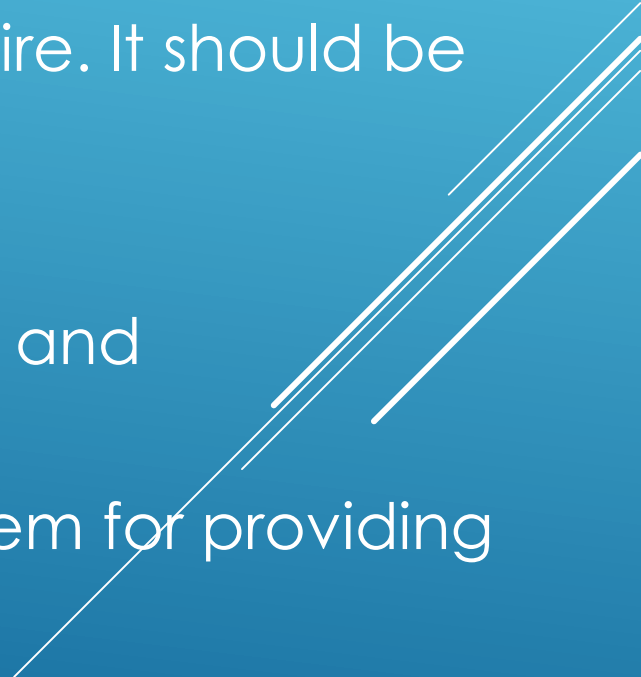
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Summary: When choosing a number of adjudicators and between internal or external members, remember 1. budget will be a main factor 2. does the sponsor or regulatory agency require external reviewers? 3. if external reviewers aren't required but desired, do you have the resources to build the infrastructure for it?

OVERVIEW OF HOW TO IMPLEMENT A CAC INTO YOUR STUDY: PLANNING STAGE

1. Develop a budget. **Possible** costs include: payment for adjudicators, payment for database development, costs for training: do you need to travel anywhere/fly anyone out/ hotel costs? If you are using a CRO to manage and implement adjudication, how much is that going to cost?
 2. Based on the budget, decide how many adjudicators to hire. It should be at least 3 experts in the field, and more if time is a concern
 3. Develop the Adjudication Charter*
 4. Decide on or develop a database for tracking agreement and discrepancies
 5. If direct access to the EMR is not an option, develop a system for providing patient case data
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THE ADJUDICATION CHARTER

*The Adjudication Charter is the fundamental document describing the Endpoint Adjudication procedure to be applied in a **specific** study*

Adjudication Charter Introduction

1. Study abstract
2. Adjudication rationale

Clinical Endpoint Committee (CEC)

3. Adjudication roles definitions

Endpoint Events

4. Endpoint definitions
5. Documents & key data to be used to define endpoints: List of source documents, variables, database from where this information is to be collected and reviewed

Endpoints Assessments

6. Process for case assignment to reviewers
7. Process for disagreement tracking and management: description of the procedures to handle disagreements among reviewers and respective resolution procedures.
8. Consensus Meeting: composition, procedures, delivery of conclusion

Adjudication Deliverables

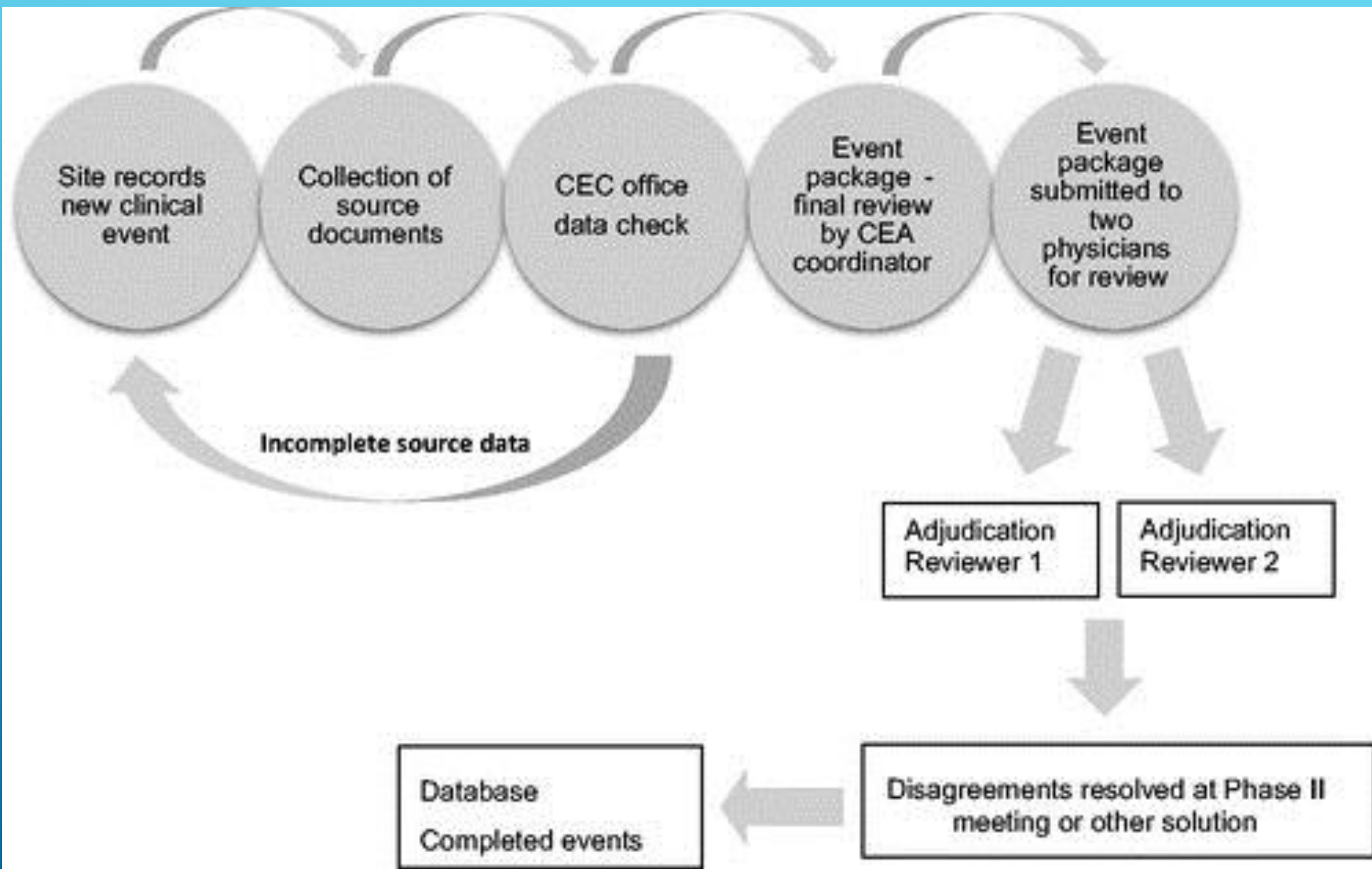
9. Deliverables to be submitted to Regulatory Authorities. Data analysis and reporting plan

OVERVIEW OF HOW TO IMPLEMENT A CAC INTO YOUR STUDY: TRAINING AND TROUBLESHOOTING

1. If using standardized endpoint definitions, train adjudicators on these definitions and on what data will be available for assessment (the entire EMR for that visit or certain variables/labs/chest x-ray etc..)
2. Test adjudicators on example cases to check for intra-variability and address any discrepancies before implementation. Adjudicators may suggest providing more/less patient case data, adjusting endpoint definitions etc.
3. Train adjudicators on the databases for viewing patient cases (if not the EMR) and entering assessments. Get adjudicator feedback on database design

OVERVIEW OF HOW TO IMPLEMENT A CAC INTO YOUR STUDY: MANAGING AND MONITORING THE PROGRAM

1. The CAC program should proceed according to what was established in the Charter. The coordinator should track that cases are being assessed, that disagreements are being addressed by a 3rd adjudicator, and by a consensus meeting if the 3 adjudicator disagreed, all in a timely manner.
2. The coordinator should conduct interim analyses to check intra and inter-reliability. If there are a concerning number of disagreements on endpoints with standardized case definitions, the coordinator should bring this up with the PI to determine if any additional training needs to be conducted.



C Held. When do we need clinical endpoint adjudication in clinical trials?, Upsala Journal of Medical Sciences, Nov 2018.

OVERVIEW OF HOW TO IMPLEMENT A CAC INTO YOUR STUDY: REPORTING

In 2009, a study in the Journal of Clinical Epidemiology found, in a meta-analysis of RCTs (n=314), that only 33.4% of studies reported their clinical adjudication methodology (Dechartres et al)

The following information is recommended by the authors for CAC reporting:

1. Report the use of a CAC in the methods section
2. Report the methods for selecting cases to adjudicate (all cases vs suspected events?)
3. Report the type of patient information provided to the CAC
4. Report the composition of the committee and the training and expertise of members in an appendix
5. Report that the CAC was blinded and independent of the trial team in the methods section
6. Report the endpoint definitions in an appendix
7. Report consensus meeting methods
8. Report any methods used to assess reliability of results

Why reporting matters: CACs are expensive, there is a lack of consensus on their value, and there is no standardized methodology. Reporting will allow for larger scale evaluations of their effectiveness

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Summary: 1. Planning is everything 2. The adjudication Charter is your guidebook: establish all definitions, protocols, and procedures beforehand in this document 3. Take time to train adjudicators on endpoint definitions AND how to use the database 4. troubleshoot early. 5. Report, report, report

ACTIVITY

You are the coordinator for a PI who has been approached by a start-up company to conduct a device trial. The company wants to submit the study results to the FDA. The company has \$60,000 for adjudication. The goal of the study is to enroll 300 patients from a sleep clinic at the PI's hospital to evaluate the efficacy of their device in detecting sleep apnea. The patient has a single study visit.

Questions

1. Will you use an adjudication committee? If so will you include internal or external adjudicators? How many adjudicators will you hire (assume \$50.00 per adjudicator per case)?
2. What are the study endpoints? Are you evaluating only for the presence/absence of sleep apnea or are you interested in the prevalence of other illnesses?
3. Develop a procedure for getting participant case data to the adjudicators. What kind of data will you provide to adjudicators for them to make their assessment?

RESOURCES

CISYS WebEAS – configurable platform for clinical adjudication entry and tracking

EPIC Web Version- if the study is associate with clinic visits and these are recorded in EPIC but adjudicators are at a different institution, you can set up EPIC groups, where you put participants records into the group and users can access only the patient charts in the group. You can get adjudicators access to this web version if they don't have an EPIC account.

Ethical eAdjudication®- configurable platform for clinical adjudication entry and tracking. You can also add patient case files to this platform if adjudicators can't use the EMR