Current State of Endpoint Adjudication in Device Trials (Industry View)

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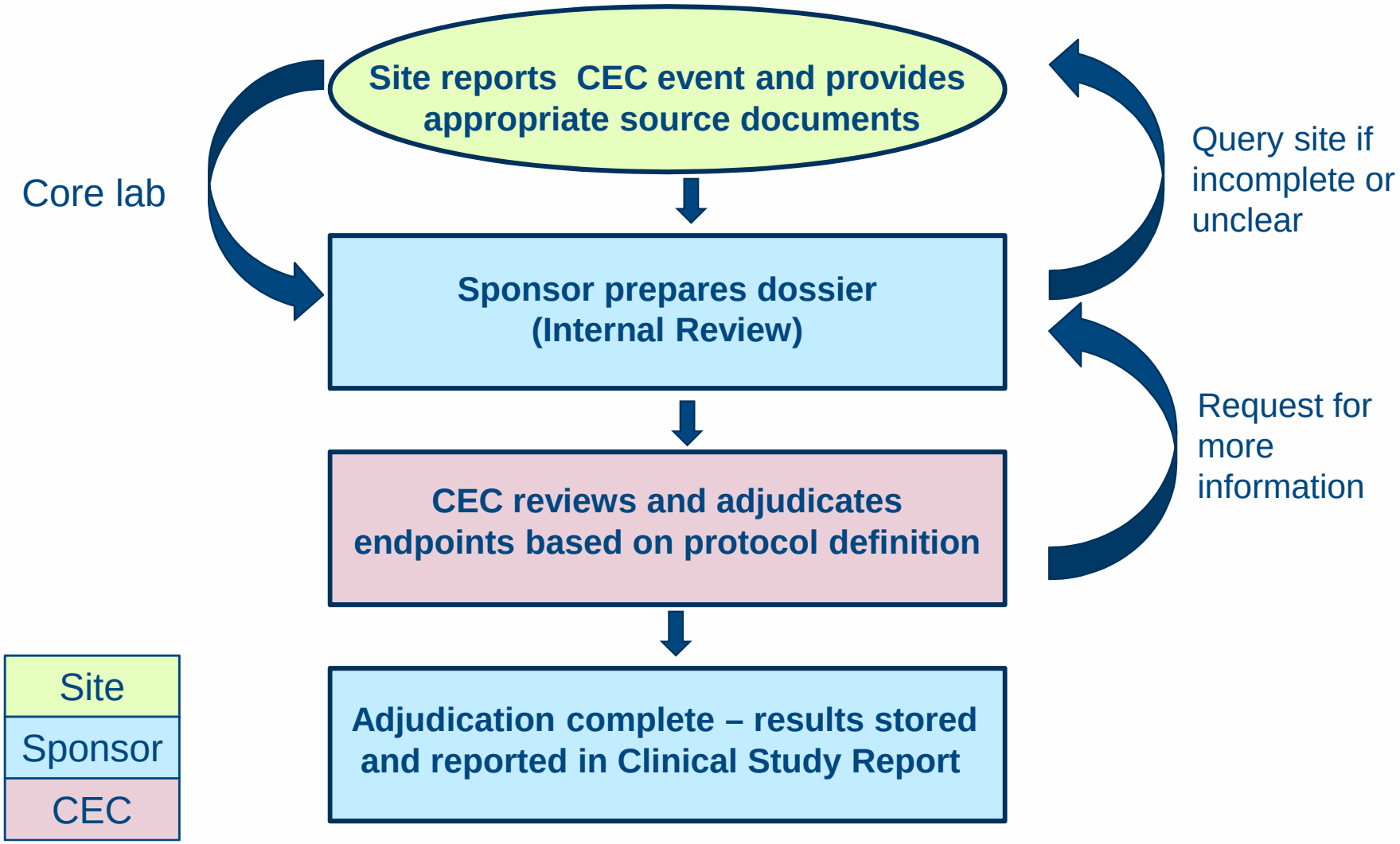
Current state: From event reporting to adjudication by Clinical Events Committee (CEC)



Current state: How Sponsor selects and trains the Clinical Events Committee (CEC)

- **Vetting of candidates** (CV, conflict of interest, past experience)
- **Orientation/Training**
  - Device Overview
  - Protocol Overview
  - CEC Event Definitions Review
  - Adjudication Forms Review
  - CEC Logistics & CEC Charter Review
- Event definitions: as much as possible use **authority defined standard definitions**
- **Safeguard independence** of CEC from Sponsor during trial

Current state: For which trials is it appropriate to use endpoint adjudication?

- ***Pivotal trial for device approval:*** Adjudication of main endpoint events in (endpoints that drive test hypotheses and typical main endpoint events) and/or major safety events
- ***Feasibility studies:*** Adjudication of typical main endpoint events facilitates poolability of data with future studies
- ***Post approval studies (less obvious benefit):*** Adjudication of typical main endpoint events improves consistency, may facilitate poolability of data across different studies and increases chances for label expansion or reimbursement

Common issues with endpoint adjudication

- **Not timely completion** of endpoint events:
  - electronic rolling database system versus paper based
  - if independent assessment pending, regular internal medical review of site and company assessment of endpoint events
- **Quality of CEC assessment** depends on quality and completeness of data provided
- **Impossible to keep CEC blinded** in some cases (e.g. valve trial, device versus surgery)
- **Endpoint definitions: ambiguity** may result in conventions decided by the sponsors resulting in inconsistencies between different sponsors
- **Delicate balance between independence and oversight**
- **Cost of independent adjudication** has to be weighed against benefit of 'faith' in the independent endpoint adjudication

Why is endpoint adjudication common in clinical trials for medical devices?

- **Increase credibility:** Independent and blinded adjudication of main endpoint events by group of experts
- **Consistent interpretation** of event definitions (global trials with **cultural differences** and differences in clinical practice across sites)
- **Consistent interpretation of softer endpoints** when objective assessments do not exist and a subjective assessment is required
- **Regulators derive confidence** in the validity of results when central adjudication is performed
- **Clinical community has become accustomed** to a certain amount of adjudication and may criticize trials that lack adjudication

What is the real benefit of endpoint adjudication and what are opportunities to streamline current state?

Difference between site/sponsor and independent CEC assessment variable, depending on trial and event type

Benefit of adjudication depending on endpoint event type (e.g. small value if the total mortality or patient-reported QoL is the primary outcome variable whereas bigger value if cardiac versus non cardiac death or appropriate vs inappropriate shock are the events of interest.)

What is the **benefit of event adjudication after core lab assessment** (e.g. TVR, TLR, remote TVR)?