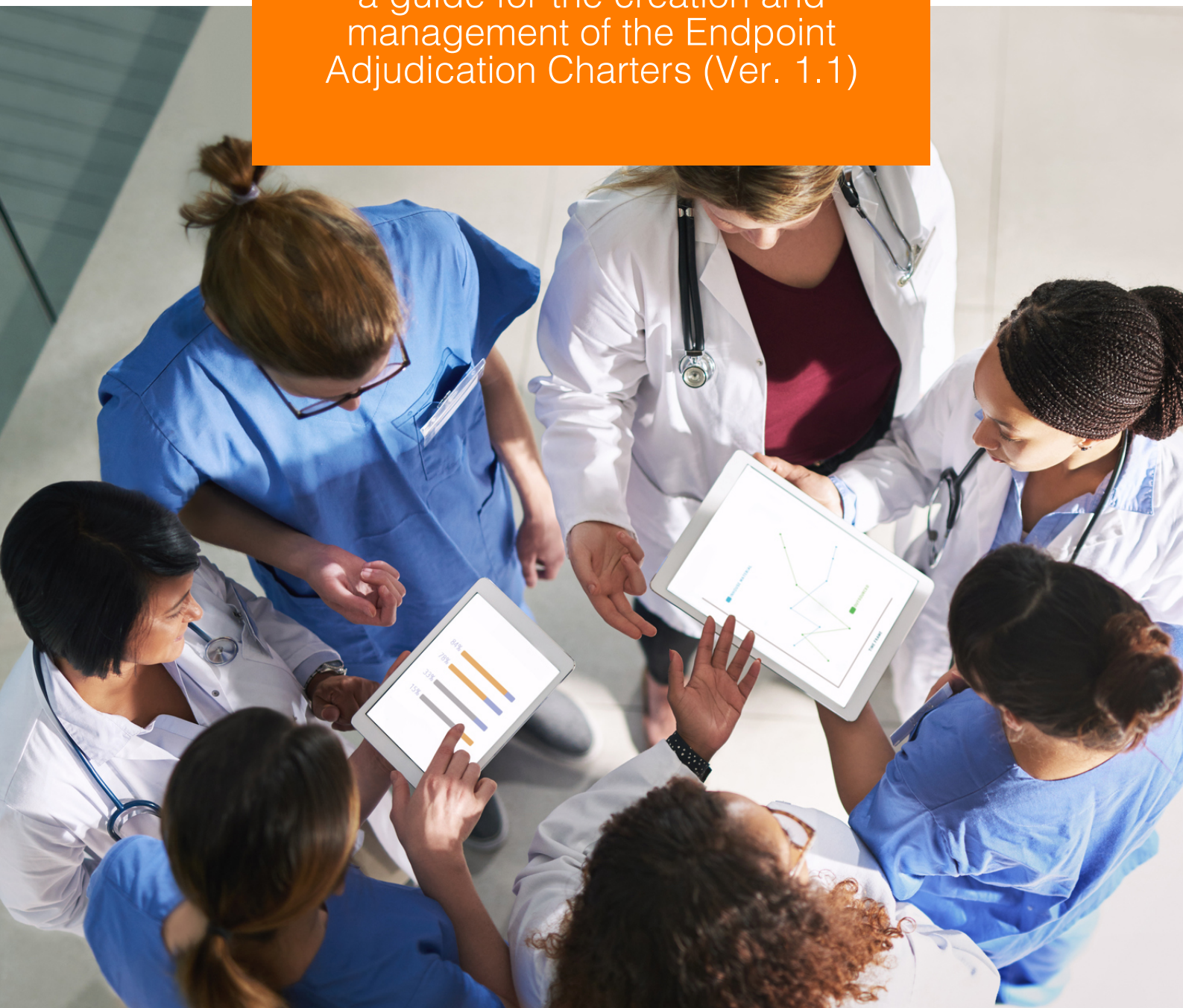
ETHICAL
eADJUDICATION

ENDPOINT ADJUDICATION CHARTER GUIDE

a guide for the creation and management of the Endpoint Adjudication Charters (Ver. 1.1)



FOREWORD

Clinical Endpoint Adjudication has been used the past years in a variety of studies and indications where the complexity and/or the subjective nature of the outcomes or the difficulty in assessing patient eligibility require a systematic, independent, blinded assessment by a group of highly specialized experts. Regulators have encouraged the use of Independent Endpoint Adjudication and in some cases included elements in guidelines and regulations.
Endpoint adjudication charters are a key element for the setup of quality Adjudication procedures and have been developed[1] in various formats. We at Ethical have performed a thorough review of dozens of endpoint adjudication charters in order to build the present guide.

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Contents of the Clinical Endpoint Adjudication Charter

1. Approval page

The Endpoint Adjudication Charter (EAC) must contain a signature/approval page where Adjudication Committee (AC) Chair and Members submit their dated signature to confirm that they have read and approved the Charter and its contents.

2. Confidentiality Statement

The header or footer of the Endpoint Adjudication Charter must contain a Confidentiality Statement.

3. Description of roles and responsibilities

The roles and responsibilities of the Adjudication Members should be described in the charter, including their responsibilities throughout the course of the clinical trial, timelines, and participation in the Adjudication Committee meetings.

3.1. Clinical Investigational Site Personnel

3.1.1. The Investigator

Provides assessment of the events

3.1.2. The Site Coordinator

Provides access to the required clinical information

3.2. Sponsor Personnel

3.2.1. Clinical Liaison

Contacts the sites for scientific information

3.2.2. Data Manager

Defines the data points to be included in the event package and the correspondence with eCRF data points

3.2.3. Statistical Programmer

Programs listings and tables including patient profiles and patient summaries to be included in the event package

3.2.4. Endpoint Adjudication Coordinator

- Ensures that all information is made available as required
- Ensures that events are reviewed in a timely manner

3.3. Adjudication Committee

3.3.1. Membership

The Charter should include a list of the Adjudication Committee Members including their contact information (work address, telephone number, fax number or email address), credentials and experience qualifying them for their assigned role(s). The criteria for selection and qualification of reviewers must be stated.

3.3.2. Disbandment of the Committee

The conditions and timing of the disbandment of the Adjudication Committee must be listed in the Endpoint Adjudication Charter.

3.3.3. Study Participation of the Committee members

Generally, the members of the committee should not participate in the trial as principal or co- investigators. If an adjudicator participates - directly or indirectly - in the study, appropriate due diligence needs to be in place by the sponsor to avoid either adjudication of self-reports or unintentional unblinding of that adjudicator. If no guarantee can be obtained, a statement must be included in the Endpoint Adjudication Charter specifying that adjudication of an event where the assessor had any involvement is nullified.

3.3.4. Meetings Conditions and Schedule

The conditions for scheduled and unscheduled meetings of the Adjudication Committee must be documented in the Endpoint Adjudication Charter. Agendas, minute and decisions must be documented by the Chairperson and archived in the Trial Master File (TMF).

3.3.5. Conflict of Interest

All Adjudication Committee members must sign a potential conflict of interest declaration.

3.3.6. Replacement of a Committee member

Procedures must be put in place in the event that it is necessary to replace a Committee Member. The Committee must document the reasons for replacing an Adjudication Committee member, such as inadequate performance and lack of communication with other members, lack of participation in consensus meetings, or inability to meet the responsibilities detailed in the Charter.

3.3.7. Documentation of the Committee work

Decision and communication are to be kept internal but are made available to auditors and regulatory inspectors.

3.3.8. Publications

Adjudication committee members' roles in authorship or acknowledgment in a publication is to be pre-specified and defined in the Endpoint Adjudication Charter.

3.3.9. Adjudication Committee Chairperson

- Chairs the Adjudication Committee meetings
- Arbitrates disagreements
- Reviews and approves meeting minutes, decisions and result
- Communicates with the sponsor / Steering Committee and clinical sites, as appropriate.
- The chairperson should as a minimum write / update or, respectively, oversee writing/updating the Charter and the decision rules.

3.3.10. Adjudication Committee Members (Reviewers)

- Review the events
- Request additional information when needed (queries)
- Return assessment to the Sponsor

3.3.11. Training of the Committee Members

All Adjudication Committee members must be adequately trained on the following:

- Study Protocol
- Events that will be adjudicated
- Procedures for reviewing
- Timelines
- Deliverables

In addition, training will describe how system access controls and blinding of reviewers will be addressed, including the processes, provisions and measures to prevent intentional or unintentional unblinding of trial participants / data. Training must be documented (signed acknowledgement) and archived (compliant with 21 CFR par 11 if archived electronically).

4. Study Information

The Endpoint Adjudication Charter should include a description of the Clinical Trial related to Adjudication, Study objectives (primary, secondary, exploratory) and the rationale for the Endpoints Assessments. The full or partial protocol may be included as an Appendix.

5. Adjudication Justification

The objective of adjudication is to invite a well-recognized group of experts in the area of the study indication to confirm that a particular event, as defined in the Endpoint Adjudication Charter took place and that it fulfills the per protocol definitions.

6. Scope of the Adjudication

6.1. Clinical Events

The Adjudication Committee is responsible for reviewing protocol-defined "events" in an independent and impartial way to ensure accurate counting, assessing, rating, etc. An event can be an endpoint (e.g., classification of the severity of a cardiac event) or a measurement of a tracing (e.g., ECG) or an image (e.g., tumor size).

6.2. Other cases

In some cases, Adjudication may be used for the independent review of patient characteristics to decide whether a given patient is eligible for inclusion in the study or fulfils the criteria for inclusion in the analysis. For the purpose of this guide, all adjudication cases will be named “events”.

6.3. Use of the Outcome

The Endpoint Adjudication Charter should state whether adjudicated results will be included in the primary data analysis.

6.4. Out of Scope

Unless defined by the Charter and supported by the composition of the Committee, review of safety signals or of benefit - risk assessments are outside the scope of the Adjudication Committee.

7. Endpoint Adjudication Software

If an Endpoint Adjudication software is used to support the Adjudication process, a description of the tool must be included in the Endpoint Adjudication Charter detailing systems' security (user ID, electronic signature, passwords to access), customization, and validation controls. The following must also be specified:

- eCRF variable to be captured by the tool
- Method for uploading documents
- Conditions for saving draft or final assessment,
- Process for linking to internal databases e.g. to upload patient profiles or listings
- System output. Screenshots of the forms must be provided in the Endpoint Adjudication Charter Appendix.

8. Endpoint Adjudication Process

The Endpoint Assessment Standard Procedures must be described in the Endpoint Adjudication Charter in a clear and unambiguous manner to support smooth, consistent and precise adjudication of clinical events or other adjudicated elements. The process must specify the timelines for each step (e.g. document translation within one working day) and these should take into consideration key study milestones and any other milestones defined in the trial protocol. If used, the process for post-hoc analyses or data re-analysis using an adjudication process must be described as well. This section of the Endpoint Adjudication Charter should include the following:

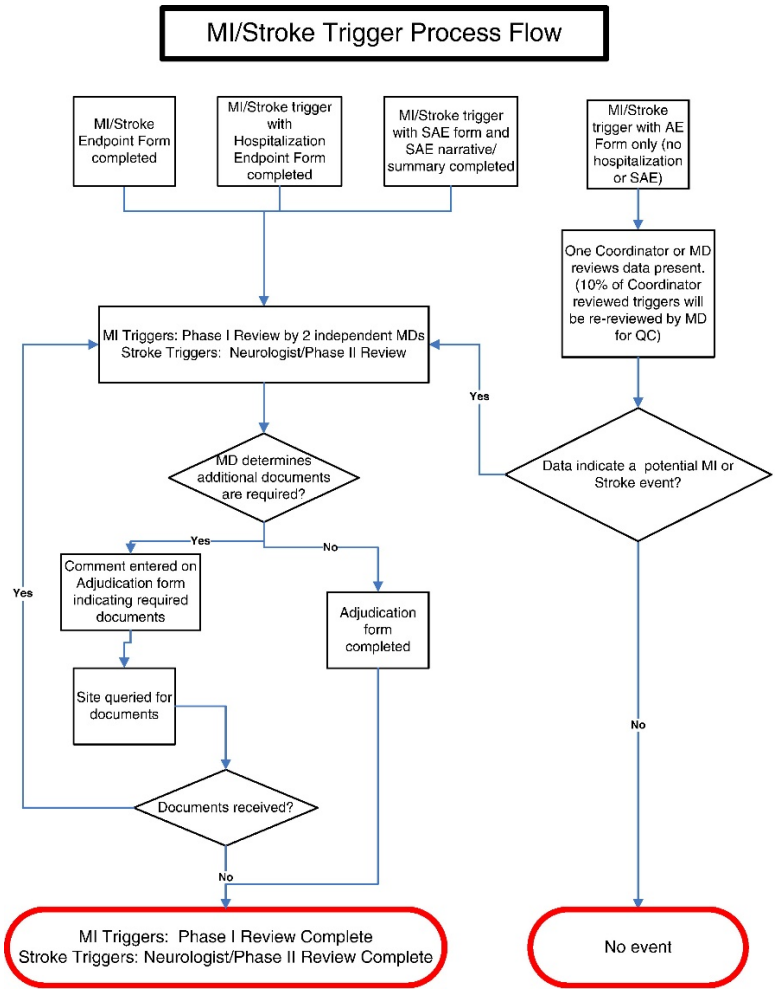
8.1. Timelines - Assessment of Workflow

The Endpoint Adjudication Coordinator should actively manage the timelines and ensure that the adjudication process runs according to the agreed plan and, where required, issue reminders to the adjudication committee members.

8.2. Chart or schema of the Adjudication process

A graphical representation of the process with decision points, actions and outcomes. An example is given below in
Figure 1.

Figure 1: Example of Adjudication Process Chart[i]



8.3. Event definitions

The following should be specified to define events to be adjudicated:

8.3.1. Definition of the events to be adjudicated

A detailed description of all events to be adjudicated must be given in the Endpoint Adjudication Charter. It must be specified if the event is a primary or a secondary endpoint of the study.

8.3.2. Data sources that will be used to define the event

The data package needed by the Adjudication Committee to deliberate must be clearly described and the sources identified. A list of documents or other material to be provided to the Committee must be given.

8.3.3. Identification codes for anonymization of the events

A description of the codes must be given

8.3.4. Blinding provisions to clinical trial site and Sponsor

The provisions for blinding the investigational site and the Sponsor to events must be described.

8.3.5. Management of patient's identifiers and relation to allocation of treatment

If needed, the treatment allocation may be linked to a patient identifier in a blinded way.

8.4. Event Management

The Endpoint Adjudication Charter will describe the sequence of events leading to the submission of an event to the Adjudication Committee including the involvement of an Adjudication software (if used) and of the different roles.

8.4.1. Methods for triggering the Adjudication process

The Endpoint Adjudication Charter must describe the conditions that will trigger the Adjudication process (e.g. Adverse Event (AE) presence in the safety database).

8.4.2. Reviewers assignment rules

The rules applied for assignment to a specific Reviewer must be described including the provisions made to avoid adjudication of self-events.

8.4.3. Preparation and transmission of the package

The Adjudication Coordinator will ensure that each package is complete including the reporting CRF and all relevant supporting source documents. This can be a paper or an electronic process. Packages are to reach the designated adjudicators independently via courier/or/electronic password protected workflows. The process shall include a step by which the reviewer can ask for additional information / data. The complete package would then consist of all original information / data plus the supplemental information / documents / data. A transmittal form must be issued to document the process and archived together with the other documentation.

8.4.4. Adjudication forms

Adjudicators must complete an Adjudication Form (paper or electronic) to return their decision. Such forms must be included as examples in the Appendix of the Endpoint Adjudication Charter. Adjudicators might send back their decisions by courier, or, register themselves in the electronic "adjudication space" especially created for that if a software tool is used. Transmittal of the assessment result bust be also documented in a transmittal form as described above.

8.4.5. Blinding and Translation

Prior to transmission to the reviewer, all documents included in the package (initial and supplementary information) must be adequately blinded as to the patient and the site of origin and, if needed, translated into English. If required, the blinded package will be routed to a certified translator before reaching the reviewer.

8.4.6. Management of Disagreements

A description of the procedures for handling disagreements among reviewers must be included in the Endpoint Adjudication Charter. The description must specify a classification of disagreement (example: major or minor, event or not event) and respective resolution procedures. If in doubt, each reviewer may request more information to make an unequivocal decision. If, however disagreement persists, the resolution must involve either the Chairperson or an ad hoc meeting.

8.4.7. Event Changed data

If an event gets re-submitted before the adjudication has been performed, only the resubmission should go for adjudication. If the re-submitted event has been already adjudicated, the last information should be re-analysed and the re-adjudication result supersedes any prior adjudication. The Chairperson may review the entire reporting, if deemed necessary.

8.4.8. Status of Events

The Adjudication Coordinator must be able to verify the status of all events and ensure that there are no events blocked in any of the steps. This is made easy with the use of Adjudication software but can also be tracked manually.

8.5. Adjudication Deliverables

The following are examples of deliverables of the Adjudication Process:

- Adjudication Assessment Report by reviewer
- Consolidated finalized Adjudication Assessment Report
- Any periodic / final summary reports
- Statement of preservation of blindness of sponsor and clinical trial centre staff members, if applicable

The format and content of these reports and the format of data and meta-data transfers / exports (e.g., as SAS, XML or other formats) must be described in the Endpoint Adjudication Charter.

9. Quality Control: data sources, procedures, analysis

9.1. Data sources

It is recommended to define media involved in the adjudication process (as data capture or as storage media) and the roles and responsibilities in entering data onto these media in a matrix table identifying explicit roles and accountabilities. A complete list of data sources and their specified format must be defined. In addition, the following aspects should be addressed:

- Data points where the CRF is the source of the entry, i.e., CRF is the source document
- Option to upload scanned data forms (PDF) or medical record elements (PDF),
- Option to upload CT or MRI imaging (DICOM)

9.2. Procedures

- Whenever relevant, the roles and responsibilities in transferring adjudication information / assessments into the CRF or clinical database must be specified (i.e. are these tasks performed by the Sponsor or his representative, the adjudicators or someone else).
- The Endpoint Adjudication Charter must describe how missing data and adjudication decisions will be tracked, solicited and finally incorporated into analyses.
- The Endpoint Adjudication Charter must describe objective criteria / rules allowing the adjudicators to refute, disregard or discount an event.
- Decision criteria and process to resolve a conflict when a clinical trial center disagrees with the adjudicators on grounds of objective evidence. (e.g. re-submit the entire file to allow the adjudicators to make a thorough, objective and educated decision).

9.3. Quality Control Mechanisms

9.3.1. Manual QC

Quality control of the adjudication may be performed on a sample (e.g. 5%) of the adjudicated events. In such cases a random selection of events can be reviewed in a QC meeting. The QC result are compared to the original result and documented in a QC report. If a disagreement occurs in key areas, the case can be re-reviewed in a new Committee meeting to render a final decision.

9.3.2. Automated QC

Software tools are able to randomly select events and re-route them for adjudication to a different or to the same reviewer. Statistics of inter and intra variability provide valuable information on the quality of the reviews, detect outliers and allow early corrections.

10. Appendices

The following Appendices may be included in the Endpoint Adjudication Charter:

- Study Protocol or Protocol Elements
- Conventions for the timing of events or other parameters
- List of Adjudication Questions and a description of the available answers for selection by Reviewers.
- List of data forms and/or data elements and how each is defined for entry purposes.
- For adjudication Committees involved in a safety / benefit - risk review, identification of the applicable RSI (Reference Safety Information) or if no RSI is available a list of anticipated (expected) adverse events as noted in previous research and how these are defined.
- Investigator Endpoint reporting manual
- Reviewer Guide
- Endpoint Adjudication Coordinator Manual

11. List of Abbreviations and Acronyms & Glossary

A complete list of abbreviations and acronyms used in the Endpoint Adjudication Charter and a glossary must be included at the beginning of the document.

12. Bibliography

[1] *Kradjian S, Gutheil J, Baratelle AM, Einstein SG, Kaslow DC. Development of a Charter for an Endpoint Assessment and Adjudication Committee. Drug Information Journal. 2005 Jan;39(1):53–61.*

[2] *Lopes RD, Dickerson S, Hafley G, Burns S, Tourt-Uhlig S, White J, et al. Methodology of a reevaluation of cardiovascular outcomes in the RECORD trial: Study design and conduct. American Heart Journal. 2013 Aug 1;166(2):208-216.e28.*

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