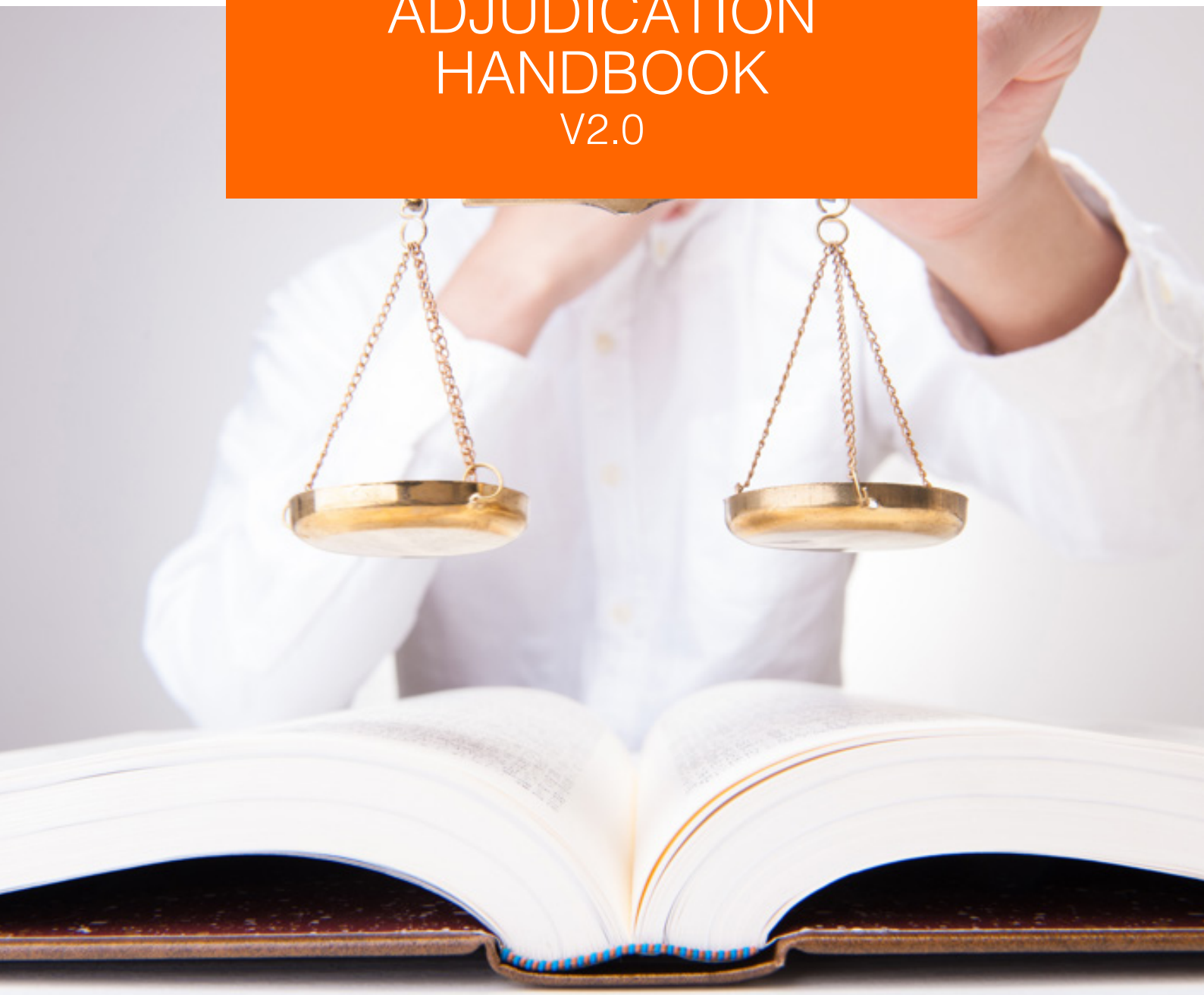
ETHICAL
eADJUDICATION

THE CLINICAL ENDPOINT ADJUDICATION HANDBOOK

V2.0



BY ETHICAL EADJUDICATION®, THE PROVIDERS OF THE ENDPOINT ADJUDICATION MANAGED SOFTWARE SERVICE
MORE INFO AND TOOLS AT HTTPS://WWW.ENDPOINTADJUDICATION.COM

FOREWORD

Traditionally, handbooks are written by experts with decades of experience and mostly used by young professional (or amateurs) who wish to have all the basic knowledge concentrated in a single publication.
But can one really speak of tradition in innovation?
And what if no one has decades of experience simply because the specific subject matter is brand new?
It then comes to some of us to take the challenge and try to group all the available knowledge under one title.
And this is what we did. We hope that this handbook will be useful to all and beg for everyone's leniency if we have omitted or misrepresented any of the content.

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1. TABLE OF CONTENTS

2. INTRODUCTION

The present handbook is dedicated to all Clinical Research professionals who are or are likely to become involved in Clinical Endpoint Adjudication operations. We hope that you will find it helpful, easy to use, complete and accurate. With this publication we hope to bring a small contribution to the common effort for a world without disease.

The FDA[1,2,3] and the EMA[4,5,6,7] have published several guidelines directly or indirectly describing the use of clinical endpoint adjudication and providing recommendations to strengthen the quality and validity of clinical data

3. CLINICAL OUTCOMES AND CLINICAL ENDPOINTS

In clinical trial we often use the terms of “Outcome” and “Endpoint”, sometimes interchangeably. For clarity, in this manual we will define the exact meaning of each of these terms.

3.1. CLINICAL OUTCOMES

Clinical outcomes are measurable changes in health, bodily function or quality of life that result from giving care to patients. Clinical outcomes can be measured by activity data such as hospital re-admission rates, or by agreed scales and other forms of measurement . The term “outcome” in clinical trials refers to a measured variable (e.g., peak volume of oxygen or PROMIS Fatigue score).

3.2. CLINICAL ENDPOINTS

A clinical **endpoint** generally refers to one of the target outcomes of the trial that can be measured objectively to determine whether the intervention being studied is beneficial but may also refer to any disease or sign that strongly motivates the withdrawal of the patient from the trial, then often termed humane (clinical) endpoint.

PRIMARY, SECONDARY, EXPLORATORY ENDPOINTS

The **primary endpoin**t of a clinical trial is the basis for making any therapeutic claims about the drug under study. All drugs have safety risks. The only reason that a patient would want to take a drug is if the drug 1) improves survival, 2) results in a benefit that was detectable by the patient (improvement in symptoms, improvement in functional capacity) or 3) decreases the chances of developing a condition or disease complication that is itself apparent to the patient and is undesirable (e.g. stroke). Therefore, a primary endpoint should be a direct measure of one of these and serve to claim an effect beneficial to the patient.

Secondary endpoints investigate additional effects of the drug and are not used to support the principle claim. Secondary endpoints are endpoints for which the trial may not be powered nor randomized. However, it sometimes happens that a secondary endpoint result indicates an important effect of the drug that later becomes its primary purpose of use.
Secondary endpoints align with secondary questions and need to be clearly defined up front. These allow to explore information obtained in the trial that may or may not provide definitive conclusions, but might guide the direction of future studies .

DIRECT AND SURROGATE ENDPOINTS

Direct endpoints are clinically meaningful endpoints that directly measure how a patient feels, functions, or survives. These are endpoints that in themselves represent or characterize the clinical outcome of interest. They can be objective: survival, disease exacerbation, clinical event (e.g. Myocardial Infarction, stroke), etc. or subjective: symptom score, "health related quality of life" (validated instrument), etc. Customarily, they are the basis for approval of new drugs.

A surrogate endpoint is a laboratory measure or a physical sign that is intended to be used as a substitute for a clinically meaningful endpoint. Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint. This expectation must be supported by strong data ("validation"). Ideally, the surrogate should exist within the therapeutic pathway between the drug and meaningful benefit i.e. the drug results in the therapeutic benefit by virtue of its effect on the surrogate.

Surrogate endpoints include a shrinking tumor or lower biomarker levels. They may be used instead of stronger indicators, such as longer survival or improved quality of life, because the results of the trial can be measured sooner. The use of surrogate endpoints in clinical trials may allow earlier approval of new drugs to treat serious or life-threatening diseases, such as cancer. Surrogate endpoints are not always true indicators or signs of how well a treatment works[10].

SIMPLE AND COMPOSITE ENDPOINTS

A **simple endpoint** measures the change of a single outcome that is meaningful in the context of the disease being studied.

A **composite endpoint** consists of at least two or more distinct endpoints, called component endpoints. Because of the need to observe a certain number of primary endpoints to achieve adequate statistical power for a study, investigators opt to use component endpoints that contribute to an overall composite event rate. This pooling of study outcomes results in higher event rates and increased statistical precision that allows designing clinical trials that include fewer patients, are less costly, and can be completed in a timelier manner[11].

WHY SHOULD WE ADJUDICATE ENDPOINTS?

Endpoint Adjudication (EA) is the procedure by which clinical events identified as potential endpoints are submitted to a panel of independent experts to be assessed in a blinded way. EA provides an independent assessment of endpoint that are either prone to variability due to different local practices (e.g. image interpretation), likely to be influenced by the investigator's knowledge of the protocol or impossible to blind (e.g. open-label study or study on medical device) and is required by regulatory authorities in the context of determined investigational settings. EA has been shown to reduce bias and variability, thus increasing the power of detection of a difference between two treatments or between active and placebo. It can therefore justify its additional cost by helping keep the number of patients enrolled in clinical trials at a minimum.

4. ENDPOINT ADJUDICATION COMMITTEES (EAC)

Clinical endpoint adjudication is performed by an independent committee of experts competent in the domain of the clinical trial and having received adequate training on the definition of the events to adjudicate, the clinical trial protocol, the adjudication charter and the tools used for exchanging information and providing the adjudication.

Endpoint Adjudication Committees (EAC), also called Event Adjudication Committee (EAC), Central Event Committee (CEC) or Clinical Event Committee (CEC). For consistence, we will refer to these committees as EAC throughout this manual. EAC are different from Data Review Committees (DRC) or Safety Monitoring Committees (SMC), follow a separate and different process for data review and may co-exist with the above in the same study.
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4.1. COMPOSITION OF AN ENDPOINT ADJUDICATION COMMITTEE

The composition of an EAC may vary in terms of number of members, expertise of the members and roles. Below are the main characteristics to be considered for a successful EAC composition.

SELECTION AND RECRUITMENT

EAC members may be selected and recruited by the sponsor, a Contract Research Organization (CRO) or be part of a specialized Academic Research Organization (ARO) providing integrated adjudication services. EAC members should not be recruited among the study investigators.

EXPERTISE

EAC members must have proven qualifications attesting of their expertise in the medical field in which the trial is investigating and must receive appropriate training on the trial methodology and focus as well as on the adjudication charter. EAC members' credentials are to be submitted to the sponsor, filed in the Trial Master File (TMF) and submitted upon request to health authorities.

NUMBER OF MEMBERS

The EAC may be composed of any number of members. However, typically 3 – 4 including the chairperson is an adequate number allowing seamless review and easy resolution of disagreements.

ROLES

The following are typical roles held by committee members:
- Chairperson
- Reviewer
- *Ad-hoc* member

At minimum the chairperson should get involved in the preparation of the EA charter together with the sponsor staff.

4.2. REVIEWERS TRAINING AND EDUCATION

All reviewers must be thoroughly trained at the beginning of the trial and, if needed, re-trained periodically for very long trials. Training must be recorded and records kept in the TMF

BEFORE ADJUDICATION STARTS

All reviewers must be trained at the beginning of the trial based on the provisions defined in the charter. If possible, a kick-off meeting should be organized (online if needed) to agree on all topics that may be confusing or unclear.

DURING THE ADJUDICATION PERIOD

For short studies the initial training should suffice but for longer trials with possible amendments, changes in the charter provisions and even in the committee composition the need for re-training committee members either individually or as a group may arise.

4.3. REVIEWERS VALIDATION

Validation is different from training. It is the verification of the reliability of each reviewer individually and the consistency of each reviewer's assessments between different reviewers.

BEFORE ADJUDICATION STARTS

Test cases can be used to verify the common understanding of adjudication rules for the particular study and confirm the consistency of responses. This step does not depend from any computerized system and can be done manually, possibly during or shortly after the kick-off meeting.

DURING THE ADJUDICATION PERIOD (INTER- AND INTRA-VARIABILITY)

Reviewers are chosen based on their high expertise and qualification. However, issues in the Charter design or in the process implementation (e.g. an unclear endpoint definition, a problem in the tools used for the measurements, an issue with the Committee composition or with the Medical Records used for the Adjudication Dossier), regional or even personal factors may lead to higher rates of variability between reviewers (intra-variability) but also in the judgement of a single reviewer over time.

Computer based systems can be of particular interest in monitoring variability and thus validating the quality of the assessments during the study by tracking performance metrics and applying simple statistical tests to different parameters. A prompt identification of unusual variability can lead to early correction of the underlying root cause.

4.4. REVIEWERS SUBSTITUTION

Occasionally, a reviewer needs to be replaced either because they are no more available or because they have been excluded by the sponsor. Such mid-trial changes should be justified and properly documented.

FOLLOWING A LEAVE

This is usually the simplest case because the reviewer can proactively give notice, possibly suggest a replacement and even participate in the onboarding training of his substitute. However, it may occur that a reviewer unexpectedly becomes unavailable due to unforeseen circumstances. In such case, the sponsor must contact the chairperson and together agree on a replacement. Subsequently the sponsor will need to plan and carry on the new reviewer's training, complete the qualification and document the replacement in the TMF and EAC documentation the new reviewer will need to review and sign the charter as well.

FOLLOWING EXCLUSION FOR LOSS OF QUALIFICATION

This is a more delicate and fortunately much rarer case. However, it does occur that a reviewer repeatedly ignores the charter's provisions or is constantly in disagreement with the investigators and the other committee members. Should a reviewer loose their qualification for any reason, the sponsor must contact the chairperson and together agree on a replacement. Subsequently the sponsor will need to plan and carry on the new reviewer's training, complete the qualification and document the replacement in the study documentation. The new reviewer will need to review and sign the charter as well.

4.5. REVIEWERS MANAGEMENT

Reviewers are hired and trained by the sponsor but must be totally free of any influence in the conduct of their role. They must have the appropriate documented qualifications depending on the nature of the disease being investigated in the clinical trial and must have no conflict of interest with regard to their role; absence of any academic, financial or personal interests is key.

CURRICULA

Reviewers' curriculum vitae (CV) must be collected and reviewed by the sponsor to verify that they have the appropriate qualification. CVs must be filed by the sponsor in the trial master file (TMF) and made available for inspection by regulatory authorities upon request. In case of major change in the reviewers' qualifications, a new version of the CV must be filed in the TMF.

CONFLICT OF INTEREST

Reviewers must sign a certificate of no conflict of interest including the disclosure of any financial interest that may interfere with their role. The certificate must be filed in the TMF.

CONTRACTS

Each reviewer must sign a contract with the sponsor, describing the nature of the work, the duration of the assignment and the financial compensation. Contracts must be filed in the TMF.

PAYMENTS

Payment will be made according to the provisions of the contracts regardless of the results of the assessments but provided that these have been delivered to the sponsor.

4.6. REVIEWERS QUALIFICATION QUALITY CONTROL (METRICS)

Beyond the academic/professional qualifications (CV) of the reviewers, the sponsor must verify that the reviewers have fully understood the object and nature of the study, have read and understood the protocol and the adjudication charter and have been trained in the use of any software tools involved in the adjudication process.

REVIEWER TRAINING

Reviewers' training must be delivered by a qualified individual (sponsor employee or another committee member) and documented in the TMF. Reviewers must sign and date training records and those must be filed in the TMF.

REVIEWER QUALIFICATION BEFORE THE STUDY START

Before the start of the trial, all documentation of the reviewers' qualification (CV, training records) must be collected, verified by the sponsor or a representative thereof and filed in the TMF.

REVIEWER INTER-VARIABILITY (SAME EVENT ASSESSMENT AT DIFFERENT TIME POINTS)

Occasionally, the consistency and quality of reviewers' work can be verified and, if needed, corrected by randomly re-assessing a previously adjudicated event. In case of discrepancy, the reviewer may be invited to compare their approach, and identify the reasons and adjust their way of working. Additional training may also be offered to clarify any misunderstandings.

REVIEWER CONSENSUS ATTITUDE

It is important that reviewers agree upfront on a consensus attitude and commit to accepting the committee or the chairperson decision in case of disagreement. This should in no way be perceived as a challenge to the reviewer's expertise or qualification but rather as a mean to comply with the trial requirements that sometimes may be different from routine medical practice.

5. THE ADJUDICATION CHARTER

The Adjudication Charter (AC) is the document describing the role, scope and process followed by the EAC for endpoint adjudication in any particular clinical trial. The EAC members (as a minimum the chairperson) must participate to the authoring of the AC and all must sign the final document and receive appropriate training. The AC must at least contain the following sections:

1. Approval page
2. Study Abstract/Proposal/Introduction Page
3. Purpose of Adjudication
4. Scope of Adjudication
5. Adjudication Committee Membership
6. Adjudication Committee Training
7. Description of Endpoint Adjudication Software
8. Adjudication Processes
9. Endpoint Assessment
10. Adjudication Deliverables
11. Communications
12. Timelines - Assessment of Workflow
13. Quality Control: data sources, procedures, analysis
14. Appendices

For more details, see the AC template in Appendix A

6. SOFTWARE & DATA MANAGEMENT

EA can be conducted in many different ways, with or without the use of dedicated software or cloud-based platforms. However, manual conduct can become very cumbersome and error prone and sponsors are increasingly turning to software solutions for the proper management of the different aspects of EA.

6.1. DATABASE & DATA MANAGEMENT

SOFTWARE SELECTION

There are several software packages on the market for the management of endpoint adjudication and numerous software tools for electronic data capture (EDC). The selection of the right tools by a sponsor should follow a standard request for proposal (RFP) process to ensure adequate coverage of the specific needs for a given trial, appropriate quality and compliance with GCP regulations.

USER REQUIREMENTS SPECIFICATIONS (URS)

The URS is the basis for development or selection in any RFP process. The RFP lists the user requirements (what the system is expected to do for the user and what a system shall not do, aka “killing-criteria”). These requirements may be functional (describing the functions of the system, e.g. “be able to store data and images”) or non-functional (describing other capabilities, e.g. “be able to support 100 concurrent users”). The level of detail of the URS is at the discretion of the sponsor. Some parts of the URS may be standardized (e.g. compliance with US 21CFRpart11 / GAMP 5, electronic records & electronic signatures) and be pre-qualified by the system vendor. The URS is the basis for the final acceptance of the system by the user.

SOFTWARE VALIDATION (ACCEPTANCE TESTS)

Before accepting the system for regular use, the users must verify the fulfilment of all and each user requirements (traceability matrix) by testing the relevant functions using test scripts and documenting the successful completion in a summary report.

SOFTWARE TRAINING

Compliance of validated systems is not limited to functional capacities (the system can do the required operations) but is also dependent on appropriate training (the users know how to operate the system correctly) and acknowledgement (the users understand the meaning and consequences of using the system). Appropriate training material must be prepared, and training delivered and documented before access is granted.

SOFTWARE INTEGRATION

Endpoint adjudication platforms perform optimally when integrated with other data processing systems such as EDC, interactive randomization systems (IxRS), databases, electronic health records (HER) etc.

6.2. EVENTS MANAGEMENT

EVENT DEFINITION

Ech trial is unique and may focus on different effects (efficacy or safety) of any given drug or device. Certain events may be of particular interest and will be selected for adjudication by an independent committee.

EVENT DETECTION AND TRIGGERING OF ADJUDICATION PROCESS

All safety-related events are recorded in the clinical safety database and, if the sponsor maintains a separate pharmacovigilance database, events categorized as Serious Adverse Events (SAE) or Adverse Events of Special Interest (AESI) also appear in the pharmacovigilance safety database. Event detection and triggering of the adjudication process may occur in different ways depending on the tools and processes used. Automatic or manual review of the clinical and the pharmacovigilance database according to the adjudication events definitions will trigger initiation of the adjudication process.

MEDDRA STANDARD QUERIES

When SAEs or AESIs are the focus of an endpoint assessment, Standardised MedDRA Queries (SMQs) can be used. SMQs are tools developed to facilitate retrieval of MedDRA-coded data as a first step in investigating drug safety issues in pharmacovigilance and clinical development. SMQs are validated, pre-determined sets of MedDRA terms grouped together after extensive review, testing, analysis, and expert discussion. SMQs have been developed with the CIOMS Working Group on Standardised MedDRA Queries that provides pharmacovigilance expertise and validation of SMQs. The SMQs are maintained with each release of MedDRA by the MSSO.

Currently, over 100 SMQs have been created and additional SMQs are created as the need arises. SMQs can be used in programming to identify events of interest in a given study and trigger the adjudication process

ESTIMATE OF % OF EVENTS TO BE ADJUDICATED

It is good practice to estimate upfront the percentage of all events that will need to go through the adjudication process in order to estimate workload overall and by period. The estimate should be compared to the actual percentage at the end of the study for future reference. The time-criticality of the adjudication process should also be identified upfront, e.g., if agreeing on the adjudication of an event is required for inclusion of a patient into a trial then this has an impact on resource management and may call for clear deputizing roles to avoid delays in patient recruitment.

EVENTS DETECTED BY CENTRAL ADMINISTRATOR OR REVIEWERS

Additional events may be identified as candidates for adjudication either by sponsor personnel (administrator, global trial leader...) or by the reviewers during the review process. These may either be special cases or they may define conditions that were missed in the initial definition. In the latter case the definitions should be updated to capture these events in the future and the Charter or equivalent document updated accordingly. When this happens, the impact of completed adjudications of events should be assessed and the outcome of such assessment be justified and documented.

RELATED EVENTS

Some events may be related and need to be reviewed in conjunction.

7. ENDPOINT ADJUDICATION PROCESSES

7.1. EVENT MEDICAL RECORDS IDENTIFICATION

SOURCE DOCUMENTS, VARIABLES, IMAGES, MULTI-MEDIA FILES

The medical records linked to the adjudicated events must be identified and listed in the adjudication charter. If during the trial additional records are identified as being of interest, the charter and any instructions or programmatic settings should be updated to include the additional definitions. When this happens the decision should be justified and documented, and all concerned party be re-trained.

OWNERSHIP OF MEDICAL RECORDS

The ownership of all medical records remains with the investigational site at all times.

SOURCE OF MEDICAL RECORDS

The source of medical records may be the patient charts or any other physical or electronic record (databases, e-archives) at the investigational site or at other healthcare sites.

FORMATS OF MEDICAL RECORDS

Medical records may be in the form of paper, photos, x-rays or electronic files of various types including videos and multimedia

TIME OF CREATION OF MEDICAL RECORDS

The date and time of creation of medical records should always be recorded.

RECURRENCE OF MEDICAL RECORDS

Some medical records may refer to recurrent measurements or repeated assessments.
The frequency and timing of recurrence should be recorded and considered during the adjudication process (e.g. verify if there is a more recent value or one that is closer to the event timing).

EXPIRATION OF MEDICAL RECORDS

Certain medical records may have an expiration date. This date should always be recorded in order to assess the need to repeat and estimate the relevance of the result for the adjudication of the event.

7.2. EVENT MEDICAL RECORDS COLLECTION

INTERACTIVE LOAD, AUTOMATED LOAD, LINKING CENTRALIZED LOAD, SITE LOAD

Depending on the method used for the adjudication process (manual, software tools, interactive platforms etc.) the collection of medical records may be done in one of several ways.

7.3. EVENT MEDICAL RECORDS ANONYMIZATION

OFFLINE / ONLINE

All medical records need to be pseudonymized and all information that could lead to the identification of individual subjects must be redacted before the record is shared outside of the investigational site. Therefore, the pseudonymization procedures must either be fully automated and validated (online) or be manually performed by site personnel (offline) prior to uploading or transmitting the records.

CENTRALIZED / DECENTRALIZED (BY SITE)

In case of automated redaction of personal information by an adjudication management platform, the operation can be centralized. In such case the original records are uploaded in a central location for processing, then destroyed. Alternatively, the process can be decentralized by site and in this case the records are processed locally and only anonymized records are transmitted to the central database.

7.4. EVENT MEDICAL RECORDS TRANSLATION

OFFLINE / ONLINE

In the event of international trials where source records may be in local (non-English) language, these must be translated before the review. Translation must follow the redaction of personal information and can either be done online by transmission of the redacted files to a translator (possibly by automatic translation / NLP) or offline by site personnel before transmission.

CENTRALIZED / DECENTRALIZED (BY SITE)

Similar to the pseudonymization process, translation can be either centralized or performed locally. In the case of centralized processing, after redaction of personal information, documents are routed to a specialized translation unit and translated versions are returned in the system. If done locally by site personnel, translation can occur at the same time as the pseudonymization and processed documents transmitted for adjudication.

7.5. EVENT MEDICAL RECORDS LABELLING

OFFLINE / ONLINE

Medical records pertaining to a specific event must be labelled as such. This can be done either offline by the site or online by the software based on pre-specified parameters.

CENTRALIZED / DECENTRALIZED (BY SITE)

The event medical records can be either labeled in a centralized way by the adjudication software or by the site in a decentralized manner.

7.6. EVENT MEDICAL RECORDS FORMAT CONVERSION

FOR READABILITY / MEASURABILITY

Medical records used in the adjudication process may need to be saved under a format which is different from that of the original record (e.g. images, scans, x-rays) in order to be viewed and/or for measures to be made. In such case, the conversion method must be validated.

FOR SUMMARIZING (PATIENT PROFILES)

In most cases, sponsors are able to produce patient summaries or patient profiles regrouping all the data pertaining to a particular patient under a single file.

FOR COMPARISON IN TIME / VERSIONING

In some cases, comparison on a time scale may be useful for the assessment of clinical endpoints. Conversion of data listings based on dates may be extremely useful for side-to-side viewing of similar data (e.g. laboratory values over time).

FOR LEVELLING OUT SITE DIFFERENCES

Different sites may use different units for the same parameter. In order to compare and regroup data from all clinical sites, it may be useful to convert units or other parameters. In such cases, the original data values must always be retained and clearly displayed to avoid reconciliation issues.

7.7. EVENT MEDICAL RECORDS PACKAGE VALIDATION

Before it is transmitted to the reviewers, an event medical records package must be validated for completeness, validity, accuracy and adequate de-identification. For this, the sponsor must:

COMPLETENESS

Verify that all necessary data are included in the package or clearly labelled “not available”.

VALIDITY (TIME)

Verify that all data available at a certain time point (as close as possible to the time of transmission) have been included in the package

ACCURACY

Verify that all data included in the package are correctly copied from available clinical records.

BLINDING

Verify that all information allowing to identify the patient, the site or the investigator has been removed from the package to guarantee the blinding for the reviewer(s).

7.8. EVENT MEDICAL RECORDS QUERYING FOR MORE INFO

BEFORE SUBMISSION / AFTER SUBMISSION

At any time, either before or after the submission of a package for review, request can be made for supplementary information. Such information must be able to be added to the package and adequate versioning must be created to avoid confusion

OFFLINE // ONLINE

The request for additional data can be done either online through the adjudication software or offline (e.g. by email or telephone). In either case, the above process has to be followed to ensure seamless data processing.

MISSING DATA MANAGEMENT

It is not rare that data that should become part of the adjudication package is missing either because it was not collected or because not included in the package. Reasonable effort must be made to retrieve any missing data and if this is not available this must be clearly documented. In case an important part of the data is missing making the assessment impossible, the sponsor must be informed as the patient may need to be excluded from parts of the analysis.

7.9. EVENT MEDICAL RECORDS UPDATE

Medical records pertaining to an event may be updated if new information is received:

UPDATES AS A RESULT OF CHANGES OVER TIME

The most frequent cause for this type of changes is more recent information has become available

UPDATES AS A RESULT OF NEW RELATED EVENTS

A new event that is related to the previous has been submitted

UPDATES AS A RESULT OF QUERIES

Additional information was added following a query by the reviewer or by the sponsor to the site.

7.10. EVENT MEDICAL RECORDS VERSIONING

DUE TO MEDICAL RECORDS UPDATES

In all cases where the medical records concerning an event have been updated, adequate versioning of the information must be performed to avoid errors and confusion. Automated versioning is most efficient but manual process may also be applied if the former is not available.

7.11. EVENT MEDICAL RECORDS DISPLAYING

VISUALIZATION TOOLS FOR TEXT, VARIABLES, DOCUMENTS, IMAGES, ETC

Case review is made easy when information is displayed in a clean and orderly way. Because of the variable nature of the collected information adequate tools for displaying different types of information are necessary. Endpoint adjudication software can fulfil these requirements if adequately configured

FOR MEASUREMENT

In some cases, measurements such as bone fracture or heart dimensions may need to be made by the assessor. The quality of the displayed images is a key factor for precise and consistent measurements.

FOR TRENDING GRAPHIC REPRESENTATION

The same applies to graphic representation (curves, bell shapes etc.). Similar graphs must be displayed in a similar manner to allow for measurement and comparison. Care should be taken in avoiding that an inappropriate selection of the scale in a graph introduces bias.

TOOLS CONFIGURATIONS

Software tools must be configured using sample images and graphics to ensure consistent display in all cases.

TOOLS VALIDATION / RE-VALIDATION

Following configuration, endpoint adjudication tools must be validated and the validation status of the system adequately documented. Re-validation may be needed during the study in case of changes to the system (e.g., substantial changes in the information displayed).

7.12. EVENT ASSEMBLING ONGOING MANAGEMENT

PACKAGES BY STATUS (COMPLETE, INCOMPLETE, TO BE LABELLED, TO BE TRANSLATED, TO BE QUERIED, WAITING QUERY RESULTS, MEDICAL REVIEW, ETC)

Endpoint adjudication software must be able to group, list and display packages based on status (e.g. complete, incomplete, to be labelled, to be translated, to be queried, waiting query results, medical review, etc.) to allow for easier management.

PACKAGES ASSIGNMENT TO STAFF

Endpoint adjudication software must be able to automatically assign packages for review based on predefined rules and/or random algorithms.

7.13. EVENT MEDICAL RECORDS COLLECTION QUALITY CONTROL (METRICS)

One of the most important features of endpoint adjudication software is the ability to produce metrics pertaining to the events management.

DELIVERY TIMING

A key performance indicator that any coordinator will appreciate.

PACKAGE COMPLETENESS

Packages completeness statistics are paramount for the assessment of the overall quality of the adjudication process.

MEDICAL RECORDS ACCURACY

Not all medical records are complete and accurate. Metrics on this parameter may allow for future better site selection and management.

QUERY RESOLUTION TIMING

Query resolution timing has been correlated to overall quality of clinical data

SEGMENTATION:

Medical records can be regrouped or segmented in different ways to support performance metrics:

- per site
- per country
- per event
- per Medical Record

7.14. EVENTS SUBMISSION / RE-SUBMISSION

ASSIGNMENT TO REVIEWERS, RULES DEFINITION

Events being submitted to different reviewers can be assigned following different rules. These rules must be defined in the charter and, if a software is used, programmed in the tool.

INTERACTIVE / AUTOMATED

Assignment may be either automated or triggered interactively by the coordinator.

FIXED / VARIABLE (BY CHARGE)

The assignment rules may be fixed or they may have the flexibility to vary based on the charge (or workload) to avoid too many cases going to any individual reviewer at a given time. This is of particular importance when completion of the assessment is time critical, e.g., assessment outcome is needed to decide on inclusion or randomization of a patient.

REVIEWERS' ALTERNATION FOR RESUBMISSION

In case of re-submission there may be a need to alternate the reviewer in order to smooth out individual differences in the assessment. However, it is advisable that the initial (e.g., baseline) and the final (e.g., end of trial) assessments are made by the same rater.

7.15. REVIEWERS ALERTING TO EVENTS

EMAIL / SMS / PHONE

Reviewers may be alerted that an event is up for review in different ways, depending on the management of the endpoint adjudication process. Email, SMS or telephone alerts are possible.

INTERACTIVE / AUTOMATED

Alert may be either triggered by the coordinator or automatically sent by the software.

PER EVENT / PER CHARGE / INTERACTIVE

An alert may be sent each time an event becomes available, when the charge shifts (e.g. too many events in a given queue) or manually

7.16. ADJUDICATION FORMS

EVENT TO FORM DEFINITION

Adjudication forms should be created for each type of event foreseen in the study.

FORM FIELDS DEFINITIONS

Each form should contain a number of fields to capture information. Those fields must be defined upfront.

FORM FIELD FORMAT DEFINITION

Information captured in the form fields must be coded in a given format defined upfront (e.g. temperature in degrees Celsius).

FORM FIELD VALIDATION RULES / ERROR MESSAGES

Clear rules for the validation of form fields must be set up-front and error messages defined depending on the possible errors.

FORMS GENERAL DESIGN

The design of the forms must be as simple and clear as possible to avoid errors and confusion.

FORMS WORKFLOWS (HIERARCHY AMONG FIELDS)

Within any given form there must be a hierarchy of fields following a logical order leading the user for ease of use.

FORM TO EVENT ASSIGNMENT RULES (INTERACTIVE / AUTOMATED)

Whenever software is used for the adjudication, the appropriate form(s) can be programmed either to automatically open or to be downloaded from a menu.

7.17. REVIEW ASSESSMENT WORKFLOW

ROLES DEFINITION

Whether manual or automated the review workflow must be clearly described in the charter and the roles of each user defined with the appropriate privileges.

ASSESSMENT WORKFLOW DEFINITION

Assessment workflows will be triggered and processed as defined in the charter

7.18. DISAGREEMENT MANAGEMENT

MAJOR DISAGREEMENT

In case of major disagreement (the definition may differ for each study), either the chairperson must decide, or the disagreement will be resolved during either a regular or an ad-hoc consensus meeting of the committee. The mode of resolution must be described in the charter.

MINOR DISAGREEMENT

Minor disagreements can be resolved among reviewers or with the help of the chairperson.

DISAGREEMENTS' MANAGEMENT FLOW

When a disagreement is detected, a predefined workflow must be triggered. Minor disagreements may be grouped for resolution during the next regular committee meeting. The adjudication coordinator must keep track of the resolution.

CONSENSUS WORKFLOW / ROLES

When consensus is needed to resolve a disagreement the workflow and roles must be described in the charter.

CONSENSUS TOOLS (PREVIOUS ASSESSMENT COMPARISON)

In case consensus is required, a comparison to previous assessments may be useful. Software tools are able to retrieve previous assessments of similar cases to help comparison and final decision making.

CONSENSUS ADJUDICATION FORMS

Specific adjudication forms must be created for documenting consensus processes and decisions.

7.19. ADJUDICATION PROCESS ONGOING MANAGEMENT

In order to facilitate the management of events, in particular in studies with many adjudicated cases, these can be regrouped and presented in different ways.

- events by status
- pending submission / resubmission
- pending query issuing
- pending query results
- pending reviews
- reviewers' queue
- pending consensus

7.20. AUTOMATED ASSESSMENT(S)

Some assessments can be automated (or semi-automated) for precision and consistency.

PER IMAGING MEASUREMENT

Where specific measurements are made in a consistent way, the operation can be made automatically

ARTIFICIAL INTELLIGENCE

Highly efficient algorithms have been developed in the recent years for the assessment of medical images. Such algorithms can be integrated in the software tools and used as decision aids for the adjudication.

7.21. REVIEW PROCESS QUALITY CONTROL (METRICS)

There are numerous metrics that can be used to assess the quality of processes used. Software tools can process and display these in very practical and useful ways.
Below are some examples:

- trends in the number of events over time
- reviewer assessment trends (always yes/no/ more data)
- reviewers intra-, inter-variability trends (comparison among reviewers)
- major / minor disagreement trend
- trends in the number of events, subject to the consensus process
- consensus results trends
- queries trends (events to queries / turn-around times for query resolution)
- segmentation:
  - per event type
  - per country
  - per site

7.22. ADJUDICATION STUDY CLOSURE

SOP DEFINITION

The charter must state which SOPs will be used for the closure of the adjudication study.

7.23. ADJUDICATION AUDIT TRAIL

Audit trail is the ultimate guarantee of data integrity within a software tool.

CONTENT DEFINITION

The content of the audit trail must be defined in such a way that it captures all key data and actions including users that perform these actions plus an unambiguous time-stamp (define the reference time-zone applied).

FORMATS DEFINITION

The audit trail must be easy to retrieve and read without the need of specific hardware or software. Tables and listings must be clearly identified.

7.24. ADJUDICATION DATA / METADATA EXPORT TO SUBMISSION

CONTENT DEFINITION

The adjudication process creates a set of data that is usually added to the clinical database and becomes part of a submission. These must be defined up-front.

FORMATS DEFINITION

The format of the adjudication data must be compatible with the rest of the clinical data and must be easy to integrate into the clinical database.

7.25. ADJUDICATION MEDICAL RECORDS EXPORT TO SUBMISSION

CONTENT DEFINITION

The charter must define up-front the content of any medical records that will become part of a submission.

FORMATS DEFINITION

As with the clinical data, the format of these records must be compatible with the format of the submission and meet eCTD requirements.

7.26. ADJUDICATION DATA / METADATA / MEDICAL RECORDS ARCHIVING

SOP

All data and metadata produced during the adjudication and all medical records used for the assessments must be archived according to the relevant SOPs.

VALIDATION

Validation documentation must also be retained as mandated by law and regulations.

LIFETIME

The length of retention of the adjudication data may vary but is usually equal to that of the other study data and documentation.

8. GLOSSARY

Endpoint Adjudication	The procedure by which clinical events identified as potential endpoints are submitted to a panel of independent experts to be assessed in a blinded way. Adjudication is used in clinical trials to manage subjective evaluations like imaging and adaptive design.
Adjudication Assessment	The core operation of an Adjudication procedure. It is usually obtained by combining the judgments of several (3 or more) Reviewers. The Assessment is collected through the adjudication forms (paper or electronic).
Adjudication Charter	The Adjudication Charter is the fundamental document describing the Adjudication Standard Operating Procedures applicable to a specific Clinical Trial. The Adjudication Charter typically includes the following sections: • Study abstract/ adjudication rationale • Adjudication roles • Endpoints definitions and identification criteria • Potential endpoints events sources • Event Package composition (documents, images, key data) • Event submission procedures • Assessment workflow and timelines • Assessment Forms structure and constraints • The procedure to request and handle “more data” for incomplete or unsatisfactory event information • The procedures to handle disagreements in Central Adjudication Committee (CEC) members assessments • The procedures to establish and run Consensus Meetings • The procedures to handle changes in the event information delivered after event’s submission to the CEC members • The procedures and trigger for Communication among Coordinator, Staff and CEC Members • Adjudication deliverables and data structures • The procedures to conduct Quality Control
Adjudication Chairperson - Chairman	The person who presides the Central Adjudication Committee and ensures procedures are followed as per Charter. The Adjudication Chairperson is often requested to resolve disagreement situations.
Adjudication Coordinator(s)	The staff person(s) coordinating all the Adjudication operations and procedures. Usually in charge of event submission to the CEC Reviewers.

Adjudication Committee	The group of persons in charge of assessment of clinical trial subjective endpoints. The Adjudication Committee is usually composed of independent expert clinicians that operate independently and are blinded to the clinical trial operations, to clinical trial center and patient identification.
Adjudication Dossier / Package Assembling	The procedures to make the Event Dossier ready for the submission to the Adjudication Committee. It usually includes the collection of Medical Records from the Site / Source Systems and their translation, de-identification / anonymizationpseudonymization, revision for completeness
Adjudication Form(s)	The form(s) used by the Adjudication Committee members to perform and record their assessment. The forms can be processed as paper or, as online fillable forms using Electronic Data Capture (EDC) provided by an eAdjudication software.
Adjudication Form(s) Edit Checks	The tools and criteria by which the inputs of Reviewers into the eAdjudication form are checked for missing, inconsistent or wrong values and other fill-in mistakes.
Adjudication Reviewer(s)	The independent experts in charge of endpoint assessment.
Adjudication Roles	The most frequently used roles are the following: • CEC Chairman • CEC Coordinators • CEC Staff – Endpoint Office (EPO) • CEC Reviewers • CEC Data Manager • CEC Quality Control
Adjudication Workflow	The procedure, as described in the Adjudication Charter, by which the Adjudication assessment is made. It is usually defined by stating: • How many coincident judgments are needed for a valid assessment? • How CEC members judgments are composed in the final assessment • What happens in case of disagreements? • What happens in case of re-submission following changes in the event information
ARO	Academic Research Organization. Typically, part of a University, publicly or privately funded, for- or not-for-profit, provide expertise in medical, scientific or technical fields.

Clinical Endpoint(s)	In a clinical research trial, a clinical endpoint generally refers to the occurrence of a disease, symptom, sign or laboratory abnormality that constitutes one of the target outcomes of the trial, but may also refer to any such disease or sign that strongly motivates the withdrawal of that individual or entity from the trial, then often termed humane (clinical) endpoint. A clinical trial will usually define a primary endpoint as a measure that will be considered the success of the therapy being tested (e.g. in justifying a marketing authorization approval). The primary endpoint might be a statistically significant improvement in overall survival (OS). A trial might also define one or more secondary endpoints such as progression-free survival (PFS) that will be measured and are expected to be met. Finally, a trial might also define exploratory endpoints that are less likely to be met.
CEC	Central Event Committee or Clinical Event Committee.
Consensus Meeting	A meeting, usually face to face, between (selected) Adjudication Committee members, to assess the events with conflicting CEC Members' judgments in the standard assessment procedure
CRO	Contract Research Organization. Perform any and/or all parts of a clinical trial on behalf of a sponsor (e.g., pharmaceutical or biotechnology company), including clinical monitoring, randomization, supply management and central laboratory management.
EAC	Endpoints Adjudication Committee, same as CEC and Event Adjudication Committee.
eAdjudication®	An online software system designed to support the Endpoint Adjudication process
eAdjudication® Legacy Integration(s)	The procedures and software systems that allow for a direct communication of the eAdjudication environment with other external and pre-existing software systems (e.g. Medidata EDC, CTMS, Oracle Argus). Integration of software is usually implemented for selection/collection of potential endpoint event information.
Endpoint Office	The central Staff that manages and oversights the Adjudication process operations. Takes care of Source Medical Records collection, translation, redaction, submission to the reviewers, queries to Sites for unreadable or missing documents.
Event's Changed Data	The situation of an event for which the related information has substantially changed. Usually, these changes lead to re-submission

Event Dossier / Package / Info	The complete set of information that is delivered to the CEC Members to support their decision about Study Endpoints. It is usually composed of documents (medical records, laboratory reports, case histories, images, key variable values).
Event Pending Adjudication	A potential endpoint event that is waiting for the CEC Committee assessment decision
Event Re-submission	The process by which the Adjudication Coordinator is submitting a potential endpoint that's has been already assessed by the Committee, for a new assessment by the Committee due to a relevant change or update in the Patient's Medical records.
Event Sources: for Medical Records	The information systems, legacy software, documents or clinical procedures from which the potential endpoint event information originates
Event Information Redaction	The process by which all the personal or site information are removed from the Event's Medical records before assembling the Event's Dossier and submit it to the Adjudication Committee. A typical operation performed by the Adjudication Central Staff to ensure the blinding of the reviewers
Event Queries	Question sent to Sites' Investigator by Adjudication Staff or Reviewers to clarify Event's Dossier information or to request a missing document.
Event Status	The current status of potential endpoint events during the Adjudication workflow. Most common statuses are: to be submitted, pending decision, to be discussed, resubmitted, changed data, close, etc.
Event Submission	The process by which the Adjudication Coordinator presents a potential endpoint, together with its information package, to the Reviewers for the assessment
Major Disagreement	The outcome of conflicting judgments made by the Committee Members about the same event. It is usually handled by delivering the event to the Consensus face to face Meeting for ultimate assessment.
Minor Disagreement	A Disagreement in the Committee Members' that relates to a lesser aspect of their assessments. Usually managed and resolved with a simple procedure to minimize impact on the study management. (e.g. the Chairman can solve the disagreement without a Consensus Meeting).
More Data Request	The procedure by which a Reviewer ask for more information about an event that he's currently not able to assess due to inadequate or incomplete information. Usually, the staff manages the requests by issuing a query to investigators/sites handling the related patient.

Potential Endpoint(s)	A Clinical Event that has the potential to constitute a Study Endpoint. Attributes that identify such a potential endpoint and the criteria that allow its detection are usually defined in the Adjudication Charter. The potential endpoints qualification as “real” Study Endpoints is made by the Committee Members and constitutes the core of the Clinical Adjudication process.
Reviewers Qualification	The procedures ensuring that every Reviewer included in the Adjudication Committee, is well qualified (with appropriate training) for the Clinical Assessments requested by the Adjudication Charter. Qualification is usually performed by submitting to the Reviewers some events with a well-known interpretation and comparing their judgements with the standard interpretation.
Reviewers Re-qualification	Same as Reviewers Qualification but applied in a later time, during the Adjudication study duration, to ensure that the Reviewer is still qualified. Failure to pass this step must lead to the Reviewer’s re-training or exclusion from the Committee.
Reviewer Intra-variability	A quality control metric of the Endpoint Adjudication procedure aimed at detecting and measuring the grade of consistency of a Reviewer’s assessments over time. It is usually calculated by re-submitting in different times the same event to a Reviewer and comparing the results to detect any discordance in their judgements.
Reviewer Inter-variability	A quality control metric of the Endpoint Adjudication procedure aimed at detecting and measuring the level of disagreement among the Reviewers. It is usually defined as a percentage of events that lead to a disagreement among the Committee Members.
(Adjudication) Quality Control	A set of procedures, measurements and metrics used to control and maintain the quality of the Endpoint Adjudication process and outcomes. It is usually performed by collecting and evaluating some specific and pre-defined metrics (Intra-Variability, Inter-Variability, etc.) throughout the study
Related Events	A set events, potential endpoints, related to the same patient, that need to be considered by the Reviewers as a single sequence of connected events even if happened in a different time.

(Adjudication) Validation Package	The set of documents used to attest that the procedures and software systems used during the Endpoint Adjudication operation are compliant with regulations (GxP, GAMP 5, US 21 CFR Part 11, EU GMP Vol. 4 Annex 11). E.g. Validation Master Plan, User Requirements Specifications, Design and Functional Specifications, Traceability Matrix, Protocols and tests scripts for Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) acceptance phases, Change Management, Backup and Recovery and Users access SOPs and procedures.
Subjective Endpoint(s)	A clinical Endpoint whose assessment requires a subjective judgement different from a simple quantitative data evaluation (e.g. evaluation of images).
TMF	Trial Master File, a collection of all critical documents attesting of the trial conduct.

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