

OFFICE OF NEW DRUGS

The Use of Clinical Source Data in the Review of Marketing Applications

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PURPOSE

- This MAPP establishes policies and procedures for the proper use of clinical source data to audit applicants' endpoint adjudication processes during the review of new drug applications (NDAs), biologics license applications (BLAs), and efficacy supplements within the Center for Drug Evaluation and Research.
 - This MAPP does not address the on-site data validation inspections overseen by the Division of Scientific Investigations (DSI), nor does it address clinical source data submitted to the Food and Drug Administration (FDA) solely for research purposes.
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BACKGROUND

- During the conduct of clinical trials, applicants collect clinical source data derived from clinical source documents to measure the efficacy and safety endpoints specified in the protocol. These values are recorded in case report forms (CRFs) and case report tabulations (CRTs) and are used by the applicant for statistical analyses. In turn, these CRFs and CRTs form the basis for clinical review staff activity.
- Although many types of clinical source data require minimal or no interpretation after collection (e.g., blood pressure, cholesterol, or other discrete laboratory values), other clinical source data types require detailed interpretation by expert clinicians to assign endpoint values (i.e., *endpoint adjudication* (e.g., examination of radiographic images to measure tumor size, or examination of hospital records or accumulated data to determine whether a myocardial infarction has occurred)). How the applicant evaluates these source data can critically affect the reported results of the trial. In most cases, it would be expected that such interpretations are made blindly, whether conducted by investigators or special assessment groups (e.g., endpoint assessment committees (EACs)). It is equally critical that there be well-described, prospectively defined, evaluation criteria. In some cases, inspection of the clinical source data by

clinical review staff may be necessary to establish the reliability of the data in the CRFs and CRTs for FDA review.

- Review of a marketing application is not complete without an assessment of the methods used to adjudicate endpoints requiring interpretation, and in many cases, it is appropriate to evaluate a sample of the clinical source data and resultant conclusions. Depending on the specific endpoints, methodology used, and a variety of other factors, the evaluation ranges from an informal review of a small number of cases to a more formal and rigorous examination of a significant sample of clinical source data and, rarely, to an actual re-adjudication of key endpoints.

The FDA maintains the authority to inspect all records relevant to the application during the NDA review process (21 CFR 314.125(b)(12)). Under the regulations cited, the FDA may refuse to approve an NDA if “the applicant does not permit a properly authorized officer or employee of HHS an adequate opportunity to inspect the facilities, controls, and any records relevant to the application.” Therefore, the clinical review staff may require an inspection of some or all source data in support of a marketing application either through an information request to the NDA applicant, or, less commonly, through on-site inspection of the sponsor, contract research organization, or clinical investigator.

However, the processes used to inspect these source data can themselves pose challenges. Evaluation of clinical source data is often subjective and, depending on the procedures used, susceptible to bias that could affect both the values of clinical endpoints and the results of efficacy and safety analyses. An FDA audit that reveals deficiencies in endpoint adjudication may trigger the need for additional evaluation of the clinical source data, but the audit itself could be biased. Therefore, just as an applicant’s methods of adjudicating endpoints should be well-defined a priori and free of bias, FDA inspection of such data also should use well-specified audit procedures, generally blinded as to treatment assignment, agreed to before the audit to minimize bias.

- On-site inspections related to endpoint adjudication may be warranted under certain circumstances. For example, review of some NDAs may raise questions as to whether proper procedures were followed on endpoint adjudication. Other examples include when re-adjudication requires special equipment only available at the clinical site to access the clinical source data, or when on-site visits are necessary to retrieve clinical source data for re-adjudication.
- In addition, FDA evaluation of some types of clinical source data in electronic format poses practical issues related to data handling and storage requirements, which also must be considered.
- Although this MAPP describes the use of clinical source data associated with the review of a marketing application, many of the principles outlined here also would apply to clinical source data associated with investigational new drug applications and drug master files.

REFERENCES

- 21 CFR 314.50 — NDAs must contain all information about the drug pertinent to an evaluation of the application
 - 21 CFR 314.102(b) — The FDA must communicate to the applicant the need for more data to facilitate FDA review
 - 21 CFR 314.125(b)(12) — The FDA may refuse to approve an application if the applicant does not permit a properly authorized Department of Health and Human Services employee to inspect "... any records relevant to the application"
 - 21 CFR 601.4(b) — The FDA may deny a BLA under these general provisions
 - 21 CFR 312.62(c) — Investigators must retain records for a period of 2 years following approval of a marketing application
 - The CDER Program Records Control Schedule is located at <http://inside.fda.gov:9003/it/RecordsManagement/RetentionInstructions/ucm155730.htm>
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DEFINITIONS

- **Endpoint Adjudication Audit** is the process of review of clinical source data by clinical review staff to assess data quality and interpretability and also assess the reliability of the process by which key endpoint values or conclusions were assigned.
- **Clinical Review Staff** as used in this MAPP refers to FDA clinical review staff in the Office of New Drugs (OND).
- **Clinical Source Data** are all measurements collected during a clinical trial that evaluate or assess a subject's clinical condition or state and comprise the components of safety and efficacy endpoints. The clinical source data referenced in this MAPP include data that must be interpreted by a clinical expert (e.g., medical imaging that requires interpretation by an imaging specialist, or histopathology slides that require interpretation by a pathologist) as well as data that must be interpreted by one or more clinicians or panels to decide that an event has occurred (e.g., cause-specific hospitalization or death; assessment of complex photographs of skin lesion to determine lesion size/number/thickness).

Examples of these records and the endpoints they support include individual tumor measurements to assess tumor response or progression, electrocardiogram (ECG) interval measurements to assess Q-T prolongation, specific clinical findings to determine the cause of death, or blood test results to identify liver injury of defined severity. These measurements may be originally recorded on CRFs, or originally recorded on other documents (e.g., laboratory reports) and then copied to CRFs and ultimately incorporated into CRTs.

- **Endpoint Adjudication** is a process of interpretation of clinical source data to reach a qualitative (e.g., was the event a heart attack?) or quantitative (e.g., did the tumor shrink by 50 percent?) conclusion about what the data show.
- **Endpoint Assessment or Adjudication Committee (EAC)** is a group of clinical experts employed to execute a standard operating procedure (SOP) for endpoint adjudication. The committee is typically blinded to the assigned trial arm when performing its assessments, whether or not the trial itself is blinded. In some cases, when there is only a single arm, the committee may be blinded as to the order of the observations.
- **Interpretation** is an activity conducted by a clinical expert or a group of experts who examine clinical source data and generate a written report of the findings or a conclusion about what they show.
- **Re-adjudication** of clinical endpoints is the process of repeating the interpretation of clinical source data to assign new values or new interpretations to clinical endpoints. When necessary, re-adjudication requires modifying the values of clinical endpoints for the purpose of reanalysis.
- A **Standard Operating Procedure (SOP) for Independent Review** of clinical source data prospectively defines the procedures that will be used to collect and/or interpret clinical source data accurately, independently, and without bias. An SOP for Independent Review may be documented as part of the clinical protocol for an individual clinical trial or may be a separate document.
- **Transcription** is the process of extracting the pertinent information from a written report (e.g., the report of clinical source data interpretation from an EAC) and recording this information in the appropriate section of the CRFs and CRTs.

POLICY

- The adjudication of clinical endpoints is the responsibility of the applicant and not the clinical review staff. Applicants should have already developed an adequate plan for endpoint adjudication, and the FDA can assist and advise the applicant during protocol design to help ensure that the interpretation of clinical source data and endpoint adjudication will be accurate and unbiased. Clinical review staff can also assist applicants in developing a real-time monitoring program to provide assurance that the protocol for endpoint adjudication is consistently followed throughout the duration of the clinical trial. The use of EACs is increasingly common, but it is also possible to train the blinded investigators to make these determinations or use local experts. An EAC is intended to increase consistency and accuracy. Clinical review staff can encourage applicants to use an SOP for Independent Review to fully describe the process to be used.
- Clinical review staff do not routinely request or accept clinical source data for review (e.g., radiographic images, hospital records), but may examine selected clinical source data, or the monitoring program, to audit the applicant's endpoint adjudication

process. Clinical review staff decide when and how to conduct an audit of endpoint adjudication on a case-by-case basis. Although some audits may be limited to an examination of a small sample of clinical source data, others may be more extensive. Clinical review staff should consider a variety of factors in determining when and how to conduct an audit. These factors include, but are not limited to, the extent to which the applicant used clinical source data to adjudicate a primary endpoint, the presence of a high degree of subjectivity in the interpretation of the clinical source data, the absence of clear and prespecified evaluation procedures, the absence of prior agreement with the applicant's endpoint adjudication process, or the awareness of potential adjudication problems based on our prior experience with the interpretation of similar clinical source data.

- The clinical review staff may, and generally should, examine a small sample of source data to gain familiarity with the nature of the data, unless the data are of a familiar sort. This examination would not be considered an audit and may be documented in the clinical review of the application. These data may not be included in the NDA submission and may be requested and reviewed on a case-by-case basis.
- If a formal audit is needed, the clinical review staff should create an audit plan, and the division director should approve the plan, before requesting access to clinical source data. This concurrence step is not intended to discourage the practice of auditing, but to help ensure a consistent approach and appropriate focus for each audit. It is not usually necessary to examine clinical source data from all subjects in a trial to conduct a scientifically valid audit.
- The audit plan should minimize the data-handling burden of the clinical review staff. It is preferable that clinical review staff use remote electronic access to the clinical source data rather than receive the data. However, remote access may not always be feasible or practical, requiring clinical review staff to physically receive the clinical source data or make other arrangements for data access. The FDA does not routinely archive clinical source data used in an audit, because the final regulatory decision is based entirely on the data contained in the application (e.g., CRTs) and not on the actual clinical source data.
- The audit should be conducted by subject matter experts in the clinical source data, and the source data should be examined in a manner that minimizes bias in interpretation. At a minimum, this review would include a blinded examination of the data.
- If the audit determines that the data in the CRFs and CRTs are not reliable enough for review because of deficiencies in the applicant's endpoint adjudication process, or in the quality of the actual source data itself, clinical review staff may conclude that a re-adjudication of the endpoints is necessary. Clinical review staff should establish acceptable re-adjudication procedures with the applicant, and the applicant is, in most instances, expected to conduct the re-adjudication and the appropriate reanalysis. Instances in which clinical review staff conduct the re-adjudication itself, excluding the applicant, should be rare and well-justified.

- When clinical review staff conduct a re-adjudication, procedures should be established to ensure accuracy and minimize bias (i.e., develop an SOP for Independent Review to ensure review by experts, such as an EAC, with no prior knowledge of the clinical source data used in the audit). These procedures should be approved by the office director, in consultation with the OND Director. The FDA must archive the clinical source data used in any FDA-conducted re-adjudication.
 - Review of some NDAs may raise questions as to whether proper procedures were followed on endpoint adjudication. In such circumstances, the clinical review staff may request on-site inspections. For example, an NDA study may report a lower than expected rate of an event of special interest. The clinical review staff may request that DSI issue an assignment for on-site inspections to ensure that the event of special interest was properly reported to the adjudication committee and that the committee followed correct procedures. Of note, such on-site inspections evaluate the *process* used by the applicant for endpoint adjudication, but do not perform actual endpoint adjudication.
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RESPONSIBILITIES

Clinical Review Staff will:

- Work with applicants to develop acceptable prospective endpoint adjudication processes during clinical trial design.
- Determine the need for an audit of the endpoint adjudication process early in the review of an NDA, BLA, or efficacy supplement. Develop and justify any need to audit clinical source data using a well-defined, prospective audit plan. Consult with others as needed (e.g., biostatistician) to develop the audit plan.
- Obtain division director approval of the audit plan.
- Identify the need for consultants for the audit. Obtain clearance of special government employees, if necessary, through the Advisors and Consultants staff. Conduct the audit and document any deficiencies.
- Convey deficiencies found in the audit to the applicant and request that it address each deficiency. Evaluate the applicant's response.
- Identify, if the applicant's response to audit deficiencies is inadequate, the need for re-adjudication of the endpoints and establish procedures for this activity, relying on the applicant to conduct the re-adjudication in most circumstances. Obtain division director approval to request an applicant-conducted re-adjudication.
- Identify circumstances in which on-site inspections may be warranted and discuss with DSI, as needed. Circumstances may include the following: to evaluate the process used by the applicant for endpoint adjudication, to view clinical source data at a remote location, or to obtain copies of clinical source data for endpoint adjudication by the review division. Draft consult to DSI.

Team Leaders and Division Directors will:

- Assist clinical review staff in establishing adjudication procedures with the applicant during clinical trial design and protocol review
- Evaluate the need for an audit of the applicant's endpoint adjudication and/or re-adjudication processes, and provide concurrence when appropriate
- Obtain office director approval for an FDA-conducted re-adjudication
- Assist clinical review staff in determining the need for on-site inspections overseen by DSI and sign off on consults to DSI

Review Division Project Management Staff will:

- Convey to the applicant:
 - Any requests to examine clinical source data
 - Any deficiencies identified in an audit
 - The need for re-adjudication for reanalysis
- Instruct the applicant to submit data, if submission of clinical source data is necessary (i.e., remote access is not possible or feasible), and designate its purpose: "For FDA Clinical Source Data Review" or "For FDA Re-Adjudication"
- Ensure appropriate consultation with DSI when on-site inspections are requested

Office Directors will:

- Evaluate the need and approve the plan for the clinical review staff to conduct a re-adjudication, in consultation with the OND Director

Office of Business Process Support will:

- Provide the clinical review staff with access to clinical source data provided for audit or re-adjudication
- Temporarily store clinical source data submitted "For FDA Clinical Source Data Review" until the audit is complete and the review division indicates that the data are no longer needed
- Archive clinical source data used "For FDA Re-Adjudication"

PROCEDURES

- During protocol review, the clinical review staff should ensure that the applicant adequately and prospectively describes how clinical source data are to be collected and interpreted accurately and without bias, and that this process is recorded in the

protocol or in a separate document such as an SOP for Independent Review. These issues should be discussed prospectively for pivotal phase 3 trials at an end-of-phase 2 meeting, and a special protocol assessment may be considered.

- To conduct an audit of endpoint adjudication during the NDA/BLA review, the clinical review staff must create an audit plan that includes, at a minimum:
 - The reason for the audit (e.g., the relationship of the clinical source data to an important endpoint).
 - The type and amount of clinical source data needed to conduct the audit. This plan should include a sound basis for data sampling to evaluate specific aspects of the applicant's data collection and endpoint adjudication. A stepwise process may be implemented in which a small amount of data can be examined initially, followed by inspection of additional data, if preliminary deficiencies are identified. Such a preliminary inspection of the data should be standard for critical endpoints. Note that sampling need not be random. The audit plan can focus on data that favor the drug at the early stages (e.g., tumor shrinkage on test drug, no effect on control).
 - The process used to examine and interpret clinical source data during the audit to minimize bias (e.g., using blinded interpretations by experienced personnel).
- The clinical review staff should discuss the audit plan with the division director and obtain concurrence. The project manager should contact the applicant and request access to the clinical source data.
- It is often not feasible or practical for the clinical review staff to receive clinical source data for an audit (e.g., the large size of the electronic files may overwhelm the FDA's ability to receive or store them); therefore, the clinical review staff should request electronic remote access to the clinical source data whenever possible. If remote access cannot be established, the clinical review staff may ask to receive only the clinical source data necessary for the audit. The clinical source data provided for FDA examination in this instance are not considered part of the marketing application and are not subject to NDA/BLA archiving policies.

In rare instances, it may be necessary to examine the clinical source data at a remote location (e.g., when the clinical source data require special viewing equipment and/or software that cannot be made available for the clinical review staff). In such circumstances, the clinical review staff will consult with DSI on whether an on-site inspection is warranted.

- The clinical review staff or designated consultants will conduct the audit. The use of consultants is recommended if the clinical review staff lack the expertise required to interpret the clinical source data.
- The clinical review staff will convey any deficiencies identified in an audit to the applicant and ask the applicant to address them.

- If the applicant fails to adequately address the audit deficiencies, the clinical review staff may request a re-adjudication of the clinical endpoints, using a mutually agreed-upon and documented re-adjudication process with the applicant to maximize accuracy and minimize bias. Usually, the applicant will conduct the re-adjudication (often by engaging an EAC), document its valid completion, and then submit an amendment to the application containing the reanalysis and amended CRTs. The clinical review staff may audit the applicant's re-adjudication.
- If the applicant chooses not to conduct the re-adjudication, the clinical review staff, through inspections overseen by DSI, may elect to obtain a copy of the clinical source data used in the audit to document its conclusion.
- In rare and justified instances, the clinical review staff may decide to conduct the re-adjudication according to the SOP for Independent Review. This decision must be approved by the office director in consultation with the OND Director, and the applicant should be informed of this decision. The clinical review staff may designate a consultant or other EAC to conduct the re-adjudication.

The re-adjudication should be conducted when:

- The clinical review staff determine that an applicant's involvement in the re-adjudication will not address the identified deficiencies
- The clinical source data were collected and provided by multiple applicants and no single applicant has access to all the data for re-adjudication (as can occur when evaluating an important safety signal involving an entire drug class)
- When review of an NDA raises questions as to whether proper procedures were followed by the applicant on endpoint adjudication, the clinical review staff may consult with DSI to determine whether on-site inspections to evaluate the adjudication process are warranted.

EFFECTIVE DATE

- This MAPP is effective upon date of publication.