



FDA Guidance on DILI New Data Requirements for All Trials

In July 2009, the FDA issued a *new final guidance defining* clinical trial *design, data and analysis requirements* for drug-induced liver injury, or DILI, cases *in all drug and biologic agent clinical trials*. DILI occurs in of 1 in 10,000 patients or less, and currently there is no way to predict what drugs may cause the condition, nor which subjects will be affected. This article highlights some critical aspects of the guidance. **All personnel involved in the design, conduct, analysis and reporting of clinical trials should read the guidance and determine how it impacts their processes.** Instructions for downloading the guidance appear at the end of this article.



Guidance Goal:

To provide information on how to identify cases of DILI and how to determine as early as possible whether a given drug or biologic causes DILI

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Cutting Edge Education

Kestrel is pleased to welcome Jonathan Andrus as a guest presenter. We are excited to share his expertise in this informative webinar.

Establishing an eClinical Vendor Management Program

Presenter: Jonathon Andrus, M.S., CQA, CCDM, VP Data and Study Operations, BioClinica, Inc.

When: Monday, January 25, 2010, 11:30 am - 1:00 pm EST

Registration: Please visit www.KestrelConsulting.com

This course provides you with information you need to establish a vendor management program to effectively qualify and manage your eClinical vendors. As organizations out-source more and more, it becomes critical to ensure that you entrust your data only to the best vendors.

After taking this course you will be able to:

- Identify the essential components of an effective vendor management/qualification program
- Understand the content and usage of the quality agreement with vendors
- Determine which vendors need to be qualified and how to manage vendors across different geographical locations

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"Great job presenting the webinar, Kit. A lot of useful information. Special thanks for posting the recording for those of us who missed it."
-Tatyana Doroshenko,
Data Manager at Pfizer

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- Understand how to prove your due diligence to the FDA with regard to vendor qualification
- Conduct audits and maintain the necessary documentation
- Develop a vendor qualification/management procedure
- Manage vendor change (software, study, IT, etc.)

Case studies and exercises bring the course materials to life and allow the participant to apply information covered during the course.

This webinar will benefit:

- Data Management Professionals
- Quality Assurance Professionals
- Clinical Managers
- Purchasing
- Outsourcing Managers
- eClinical Vendors



What You Will Get

- 75 minutes of lecture
- Slide deck with all materials used during the webinar
- Tools to help you, including a paper audit checklist, on-site audit checklist, pre-audit questionnaire, and audit request form
- Q&A opportunity with an industry quality expert
- Post-webinar quiz (voluntary) to check your understanding of the material.

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Standards Management 101 Series

Duration: 7 webinars; each is a 75 minute lecture, plus 15 minutes Q&A

Presenter: Kit Howard, MS, CCDM, CRCP

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Definition of Drug-Induced Liver Injury (DILI):

Severe liver injury (i.e., irreversible liver failure that is fatal or requires liver transplantation) caused by a drug or biologic agent

Diagnosis:

DILI is very rare (about 1:10,000 subjects), and thus will not show up in very many clinical trials. Many mostly unknown factors seem to influence whether an individual will develop DILI. The guidance extensively discusses the diagnostic criteria, their specificity and sensitivity, and their interpretation. The basic diagnostic criteria in the guidance follow Hy's Law and are:

- Aminotransferase (ALT or AST) levels ≥ 3 times upper limit of normal (ULN)
- Serum total bilirubin level (TBL) levels of ≥ 2 times ULN, with or without significant ALT/AST elevations
- No other apparent reason for the elevations (e.g., viral hepatitis, underlying liver disease, or other hepatotoxic drug)



Data Capture Requirements:

For subjects who meet the above criteria, significant amounts of data are required. While most of these data points are familiar, most studies either do not capture them routinely or in as much detail as now required. They include:

- Duration between the most recent concomitant medications and the onset of DILI (including alcohol, herbal supplements, alternative treatments, and recreational drug use)
- Extensive medical history including concurrent conditions, especially focused on potentially liver-related conditions (including special diets)
- History of exposure to environmental agents
- Complete description of DILI symptoms
- Complete description of treatment and outcome
- Free text describing the course of the subject's case

The guidance states that the data must be included in "the clinical database," but this does not necessarily mean the study clinical database. These data could be handled like serious AE data and stored in an alternative database, reconciled with the study database, and merged in later.

Identifying the lag between each concomitant therapy and the onset of DILI may be a challenge. The guidance states that CRFs should capture both date *and time* of the concomitant medications. Since we don't know who will develop DILI, this implies that we should collect it for every subject. As the condition is extremely rare, most of the data would never be used. This does not seem to be an optimal solution. We may need to rethink our assumptions

around what is captured prospectively vs. retrospectively, what is captured on traditional CRFs vs. specialized CRFs (or perhaps other methods), and where and how the data are stored.

Data Analysis Requirements:

The guidance states that analysis of the DILI data should include:



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FDA Guidance on DILI cont.

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- Evaluation of the metabolic pathways of the drug (most hepatotoxins utilize the CYP450 pathway)
- Comparison of subjects with mild as well as severe symptoms between control and treatment groups
- Investigation into possible related factors such as sex, age, underlying diseases, and concomitant treatment regimens.
- Identifying risk factors that may lead to predictive models.

Data Reporting Requirements:

Study reports should include discussions of the above analyses as well as narratives of each affected subject. The guidance lays out specific information that should be included in each narrative. Most, but not all, of these data points are specified in the CRF section of the guidance.



Significant Points:

Pooling Phase I trials with Phase II, III and post-marketing: an analysis of the incidence of liver-related AEs should be included in each submission. This should include all trials. This is the first time (as far as the writer is aware) that Phase I data from healthy volunteers is to be pooled with data from patients.

Inclusion of liver-impaired subjects: the guidance asserts that subjects with stable liver disease are usually excluded from clinical trials, but that the disease alone is not a sufficient reason for exclusion. Some such subjects should be included if the drug is likely to be used by this population after approval. This may change eligibility requirements for some studies.

Expedited reporting requirements: Subjects meeting DILI criteria should be reported to the agency similarly to SAEs. This may require a change in process as each DILI diagnostic criterion by itself may not constitute a Serious AE.

Physical exam findings: the description of the CRF free text data requirements and the subject narrative in the study report both include discussing physical examination findings, particularly those that relate to liver abnormalities. CDISC CDASH (data capture) recommendations currently state that physical exam findings should appear on either AE or medical history forms, and that capturing the exam findings *per se* on a CRF is not necessary. The DILI guidance may or may not require a reassessment of this position, but the findings listed by the guidance as being worthy of inclusion (e.g., hepatomegaly, splenomegaly, right-upper quadrant tenderness) are all conditions that would be reported in other domains (e.g., AE) if identified during the trial. Therefore, in the opinion of the author, the inclusion of a physical examination CRF should not be necessary.

To Download the Guidance:

The formal title of the guidance is “Drug-Induced Liver Injury: Premarketing Clinical Evaluation.”

It is available at this link:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>.

It can also be accessed from:

www.fda.gov

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Article by Kit Howard



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