Time Course Graphics for Individual Subjects in DMC Reports

Brian Traver and Melissa Schultz
Statistical Data Analysis Center, University of Wisconsin, Department of Biostatistics and Medical Informatics

A Data Monitoring Committee (DMC) is responsible for the monitoring of patient safety and treatment efficacy of ongoing clinical trials. Interim DMC reports provide analyses in the form of tables and graphics that are frequently aggregated by treatment group.

The Statistical Data Analysis Center (SDAC) at the University of Wisconsin-Madison specializes in producing interim reports and analyses for DMCs. Our reports are graphically based, allowing DMC members to easily identify differences between treatment groups or changes over time, and to review a large amount of information in a short amount of time.

DMCs may also require subject-level presentation of data in order to look more closely at particular cases of concern. For example, an aggregate graphical view of laboratory data such as box plots may reveal outliers suggesting hepatotoxicity but provide no additional information. Plots displaying multiple types of data over time, such as laboratory results, adverse events, and dosing, for individual subjects, may provide additional insight into the possible underlying pathology. Concurrent elevated liver enzymes could indicate drug-induced liver injury; however, elevated liver enzymes could also occur in the presence of viral hepatitis. These patterns, lost in aggregate analysis of a single parameter, are revealed in the subject-level graphical presentation.

Here we present examples of graphics for individual subject data with features that we have found useful for DMC reports. Types of data displayed may include demographics, subject disposition (on treatment, discontinued treatment, completed study, death), dosing, event data (adverse events, positive antibody test results), and continuous measures (laboratory test results, bone density). Relevant text, such as a list of adverse events, may be presented adjacent to the graphic panel.

For more information about SDAC, including a link to a sample DMC report, please visit our web site:
https://www.biostat.wisc.edu/content/clinical-trials-statistical-data-analysis-center-sdac

Example 1: Liver Function Test Elevations

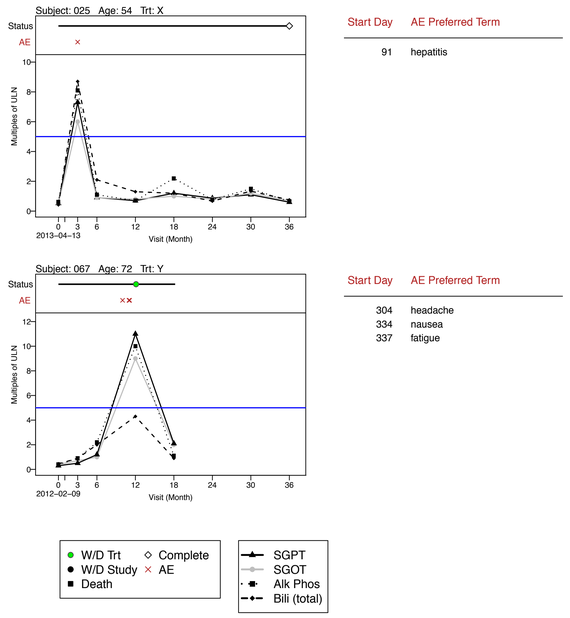
Drug-induced liver injury is often a concern in the monitoring of clinical trials. This display shows the levels of four laboratory measures that evaluate liver function: serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), alkaline phosphatase and bilirubin.

Test results are represented as multiples of the upper limit of normal (ULN) so that they can be displayed together with a common y-axis.

Several questions considered by DMCs may be addressed with these time course displays:

- Do multiple tests have concurrent elevations?
- Does an elevation persist, or return toward normal after the peak value?
- Were any adverse events associated in time with the abnormal lab test results?
- Do elevations occur in conjunction with a liver disease not suspected to be caused by the drug, such as viral hepatitis?
- If the protocol states that study treatment should be stopped following a specified LFT elevation, did that in fact happen?

Subjects with SGOT or SGPT > 5x ULN

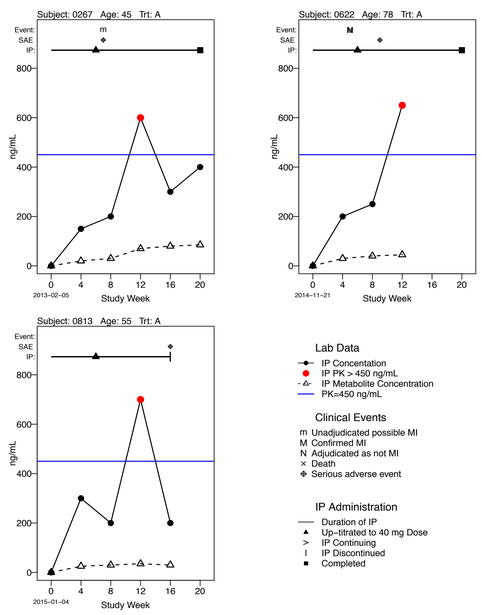


Start Day	AE Preferred Term
91	hepatitis

Start Day	AE Preferred Term
304	headache
334	nausea
337	fatigue

Example 2: Pharmacokinetic Monitoring

PK Values for Subjects with an IP Plasma Concentration > 450 ng/mL



If pharmacokinetic (PK) data are being measured during a trial, the DMC may have the opportunity to review PK values in their unblinded reports.

This example represents a trial with a planned dose increase of the active treatment (indicated in the IP status line). There is a potential safety concern if PK concentrations rise higher than expected; thus, a desire to examine subject-level PK and other data for cases in which a value exceeds a chosen threshold.

Symbols and lines represent concentrations of the IP compound and its major metabolite over time. Measurements have the same units and y-axis.

A horizontal line indicates the threshold of concern; values above it are highlighted with color and larger size.

Possible questions that may be addressed during review:

- Did the elevation occur while on the low or high dose?
- Does the metabolite level follow the IP concentration in an expected pattern, making it seem more likely that a high value is real and not due to a laboratory error?
- Are any SAEs or cardiac ischemic events associated with the high PK levels?

Example 3: Cardiac Biomarkers

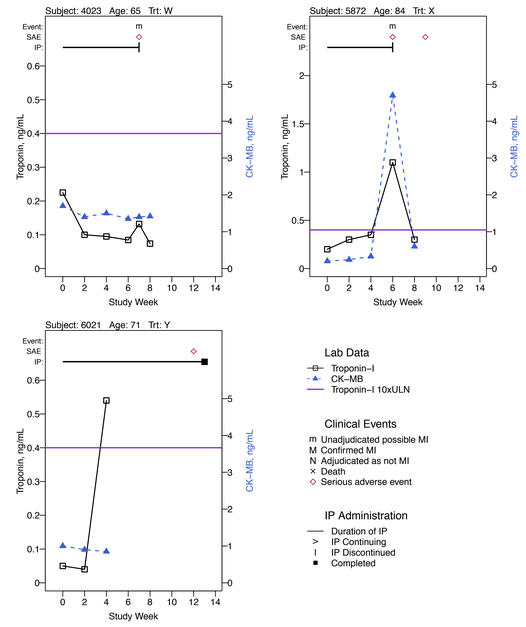
In a study of cardiovascular disease, cardiac biomarkers may be measured as part of the scheduled laboratory testing. For this example, the focus is on troponin elevations and a possible association with cardiac ischemic events (primarily myocardial infarction, MI).

A DMC may identify a set of subjects for whom they wish to examine data more closely; in this case, the criteria are ever having a troponin value above 10 times the ULN (marked by the horizontal line) and/or a potential MI event, whether adjudicated or not.

CK-MB is measured at the same visits as troponin, and its values are displayed with a separate y-axis label and scale. Seeing whether the two biomarkers increase together or vary independently may suggest different possibilities for the underlying cause or clinical implications.

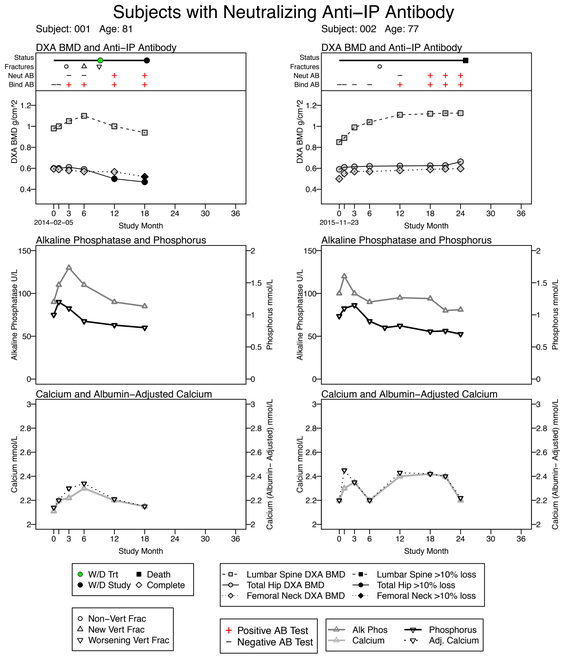
Other considerations could include whether high biomarker levels potentially reflect an increased risk of events of concern, or occur more frequently in one treatment group than another.

Troponin–I and CK–MB for Subjects with a Troponin–I > 10xULN or a Potential MI Event



Example 4: Bone Mineral Density and Fractures

Subjects with Neutralizing Anti–IP Antibody



A DMC monitoring an investigational product (IP) that increases bone mineral density for the purpose of reducing fractures may want to see the subject-level data over time for subjects that have neutralizing anti-IP antibodies.

This display indicates non-vertebral, new vertebral and worsening vertebral fractures along with negative or positive anti-IP antibody status. The presence of neutralizing antibodies could indicate an attenuation of the effect of the IP leading to the reduction or lack of increase of bone mineral density as indicated by the dual-energy X-ray absorptiometry (DXA) displays.

Also displayed over the same time course are serum alkaline phosphatase, phosphorus, calcium, and albumin-adjusted calcium, which may indicate bone metabolism.