CFF DMC Report Guide

This document presents a guide to content for the safety monitoring reports reviewed by Data Monitoring Committees (DMCs) whose members belong to the Data Safety Monitoring Board (DSMB) of the Cystic Fibrosis Foundation (CFF). The goal in drafting the document was to provide a general report template of easily implemented presentations for consideration by Study Sponsors, DMC members, and those from the organization responsible for preparing the DMC reports when planning the DMC report for their specific study. While this guide's content recommendations would be suitable for most studies, those who are planning the DMC report should modify and add presentations as appropriate on the basis of the specific needs of any given study. The final version should be agreed upon both by the study team and the DMC to ensure that the report meets the needs of the DMC and is reflective of the study.

The DMC needs to receive clear, easily reviewed interim reports that highlight any safety or quality concerns. Overly complex or difficult to read presentations of data can obscure important information leading to ineffective monitoring. Although the greatest concern is the impact on safety and quality monitoring, these reports can also lead to delays in the process and added cost for the sponsor or contract research organization (CRO). By pro-actively integrating the DMC into the reporting planning these challenges can be avoided.

It is the responsibility of the unmasked study statistician to summarize relevant findings in regard to not only any pre-specified group sequential monitoring, but also, and more likely to occur, a discussion of relevant findings in terms of imbalance in enrollment or terminations, study conduct/integrity issues, imbalance in lab abnormalities, imbalance in AEs, SAEs, AESIs and other key parameters. This responsibility doesn't preclude the DMC's task to review the data, but it is expected to reduce the risk of safety signal estimates being lost in a lengthy report, i.e., avoiding the 'where's Waldo' effect.

The document provides several sample presentations that are hyperlinked within each report section. For smaller studies or DMC reviews that occur early in the trial, those preparing the DMC report should consider replacing listings for tables or figures when data are sparse.

Although the prototype presentations in this document label the treatment arms as 'Group A' and 'Group B', at each of its reviews the true (unblinded) identities of the treatment arms that correspond to each label should be conveyed to the DMC in a secure manner.

Table of Contents

1. Executive summary

Displays and a written report are required for this process. The narrative is expected to be developed by the unblinded statistician. The report should either i) begin with a table that summarizes the most salient details or ii) include bullet points with a more detailed table appearing subsequently in the document. Generally, each study variable should be reported to the number of decimal places suited to the nature of the measurements, e.g., lung function as measured using FEV_1 % predicted should be reported using one decimal place. Percentages typically should be reported using whole numbers, but low percentages (single digit) may warrant including one decimal place, e.g., 0.5%. The DSMB leadership and/or DMC Chair should work with the report's preparer prior to the DSMB's organizational meeting to discuss the content of the executive summary. If needed, reporting recommendations may change at the organizational meeting; however, following this guide and working with the DSMB leadership/DMC Chair prior to the organizational/initiation meeting should reduce the likelihood of this occurring. For interim reports after the first, we recommend that the previous report's executive summary be provided, allowing the DMC to compare changes in important details that have occurred in the time between the two reports. An example executive summary table follows.

	Group A *n (%)*	*Group B* *n (%)*
Randomized as of <date>	xx	xx
Received at least one dose of study drug	xx (xx)	xx (xx)
Still on study treatment	xx (xx)	xx (xx)
Permanently discontinued study treatment	xx (xx)	xx (xx)
Discontinued from study	xx (xx)	xx (xx)
Reporting an SAE	xx (xx)	xx (xx)

1.1. Protocol/Interim Review Summary

A summary of the protocol and goals of the interim review should be briefly provided here, capturing/reiterating the essence of the sponsor/CRO open report PowerPoint. The summary

should provide a high-level review that refers to the charter as appropriate without directly copying and pasting from the charter document. Predefined criteria for stopping guidelines to be used for interim analyses (e.g., stopping early for futility or efficacy for a primary outcome, stopping early due to certain types or rates of AEs, etc.) and past substantive amendments to the protocol do not need to be reexplained in this section but should be referenced.

1.2. Past Executive Summaries with DMC Recommendations

The past executive summaries can be provided for ease of evaluating the progress and details of the trial. The DMC recommendations accompanying the prior executive summary should be provided to allow further context of past decisions made with regard to the study.

2. Study recruitment

Suggested content

- Screening status and reasons for screen failure (Table 1)
- Actual and estimated randomizations by study month, including triggers for DMC meetings (Figure 1)
- Randomization by country and/or study center (Table 2)

3. Data availability

Suggested content

- Compound bar chart of data availability by scheduled study visit (Figure 2)

4. Study Conduct

Possible content

- Tabular summary of protocol deviations/violations by type (Table 3): The definition of each deviation and violation should be clear in the protocol.
- Tabular summary of rate of protocol deviations/violations by study center

- Listing of protocol deviations/violations: Because any tabular summary may lack the verbatim description of each deviation or violation, the DMC may wish to have a listing available that would contain these details.
- In the unlikely event that a corrective and preventive action plan (CAPA) is needed for an event or overall site performance, this should be presented in summary form.
- Quality control/operational statistics should be described in the DSMP within the Study Charter. Associated reports should be included with meeting materials with discussion of any reports identifying potential issues/problems.

5. Baseline characteristics

Recommended content

- Demographic characteristics
- Prior disease history – e.g., medical history summarized by system organ class and preferred term
- Disease-specific baseline characteristics – because these vary by study and indication, this document does not provide a mock-up of the disease-specific baseline table(s). At a minimum, it should include a summary of any baseline factors identified as subgroups of interest in the protocol or analysis plan.
- Prior/baseline characteristics selected for the report should be relevant to disease history and are expected to be sponsor dependent. Commonly, this includes conditions within either 12 or 36 months. The timeframe should be consistent with the study timeframe.

6. Subject disposition

Example tabular summary of Subject status (Table 4)

7. Study treatment exposure

Example tabular summary of Study treatment duration and dosage modifications (Table 5)

8. Adverse events

Because the length of the adverse event (AE) section of most reports, we suggest starting the section with an overview table of the AEs followed by a tabular summary of AEs as classified according to the 27 MedDRA system organ classes. This would help orient the reader for the AE tables by MedDRA preferred term that follows. Selection(s) of these terms should be DMC and/or study-specific. Thoughtful consideration of HLT, preferred or group terms is encouraged, particularly before the organizational meeting between the sponsor and DMC.

Recommended content

- Overview of adverse events (Table 6). Use of rates is study-dependent and should be discussed when creating the report template. Studies with sufficient events and follow-up of at least 6 months may be useful settings to report rates but may not be informative in instances with rare events.
- Dot plot and relative risk plot (Figure 3): The DMC can quickly assess each in terms of occurrence and relative risk between groups.
- Volcano plot (Figure 4): The DMC can view risk difference between groups with categorization according to statistical significance (adjusted using false discovery rate; adjustments may be subject to decisions made by the DMC and study team in when developing the DMC's report template).
- AEs by system organ class (Table 7). A shorter version of this table could be reported only including AEs with sufficient prevalence in at least one of the groups, e.g., at least 10%. Reporting terms in alphabetical order may be preferrable depending upon DMC and sponsor preferences.
- Serious adverse events (Table 8): The DMC should consider whether it wishes also to have access to some or all of the available narratives for SAEs including CIOMS (Council for International Organizations of Medical Sciences) forms. The sorting method should be explicitly stated for the table.
- Grade 3+ AEs (similar layout to Serious adverse events in Table 8)
- AEs of special interest (AESI) (similar layout to Serious adverse events in Table 8): the sponsor and DMC may consider prespecifying AESI either prior to or at its

organizational meeting on the basis of the treatment's mechanism of action or past studies or potential risk profile.

- All AEs (similar layouts in Serious adverse events, Table 8; dot and relative risk plots, Figure 3; volcano plot, Figure 4). See above comments regarding AE selection and sorting.
- AEs leading to modification of study treatment (similar layout to Serious adverse events, Table 8)

9. Clinical laboratories

Recommended content

- Summary of clinically significant laboratory abnormalities in follow-up (Table 9)
- Liver enzyme elevations, Table 10 (Hy's Law summary): For those with noteworthy elevations, by-patient plots or spaghetti plots of values over time could also be generated. Hy's Law graphic (Figure 7) is recommended.
- Shift plots (Figure 6) or scatterplots of maximum (or minimum, if appropriate) versus baseline laboratory values for ALT, AST alkaline phosphatase, total bilirubin, and other data; color-coding out-of-range observations and including grid marks.

10. Vital signs, ECGs, and respiratory function measures

Boxplots should be used to summarize vital signs and measures of respiratory function such as FEV_1. This may apply to other monitored values depending upon the intervention being studied and its risk profile; e.g. if a study drug might alter calcium metabolism then boxplots of calcium and phosphorus levels would be useful.

If ECG data are collected, this table provides a sample of how these data could be summarized categorically: Summary of notable ECG changes from baseline (Table 11)

Alternatively, spaghetti plots may be useful to view changes within and between subjects over time or study condition. The DMC and sponsor should determine a priori the lab variables to

be presented as spaghetti plots and how to properly flag subjects or out-of-range values/changes.

11. Efficacy

Because efficacy assessments will vary by study, this document does not provide prototype presentations of them. However, boxplots or other graphical summaries could be used to descriptively summarize continuous efficacy endpoint data. Generally, DMCs should have the ability to access efficacy data to allow assessment of potential offsetting benefits of therapy in the context of observed risks that the DMC may identify its safety monitoring role.

Example presentations

TABLES

Table 1. Screening status and reasons for screen failure*

	n (%)
Screened subjects	**xx**
Completed screening and randomized	xx (xx)
Screening ongoing at the time of data cut-off	xx (xx)
Failed screening	xx (xx)
Reason for screen failure	
Reason 1	xx (xx)
Reason 2	xx (xx)
Etc.	xx (xx)

*Information presented here may already be included in high-level disposition table. The need to create this separate table should be determined by the DSMB and Sponsor.

Table 2. Randomization by country and study center*

Region/ Country	*Group A* *N=XXX* *n (%)*	*Group B* *N=XXX* *n (%)*
Region 1	**xx (xx.x)**	**xx (xx.x)**
Country 1	xx (x.x)	xx (x.x)
Site 1	xx (x.x)	xx (x.x)
Site 2	xx (x.x)	xx (x.x)
Country 2	xx (x.x)	xx (x.x)
Site 1	xx (x.x)	xx (x.x)
Region 2	**xx (xx.x)**	**xx (xx.x)**
Country 1	xx (x.x)	xx (x.x)
Site 1	xx (x.x)	xx (x.x)
Site 2	xx (x.x)	xx (x.x)
Etc.	xx (x.x)	xx (x.x)

*For studies that are not multinational, region and country can be omitted

Table 3. Tabular summary of protocol deviations/violations by type

	Group A N=XXX n (%)	*Group B N=XXX n (%)*
Subjects with any major protocol deviation/violation		
Cumulative	xx (xx)	xx (xx)
Since last reporting period	xx (xx)	xx (xx)
Procedural	xx (xx)	xx (xx)
Safety assessment not performed	xx (xx)	xx (xx)
Efficacy assessments not performed	xx (xx)	xx (xx)
Out of window visit	xx (xx)	xx (xx)
Exclusion	xx (xx)	xx (xx)
Received prior prohibited medication	xx (xx)	xx (xx)
Ineligible FEV1 (% predicted)	xx (xx)	xx (xx)
Other	xx (xx)	xx (xx)
Inclusion	xx (xx)	xx (xx)
Informed consent	xx (xx)	xx (xx)
Other	xx (xx)	xx (xx)
Medication	xx (xx)	xx (xx)
Received incorrect study medication*	xx (xx)	xx (xx)
Received prohibited concomitant medication	xx (xx)	xx (xx)
Study drug not interrupted/discontinued as required by protocol	xx (xx)	xx (xx)

*Denotes major protocol deviation/violation (produces actual harm to a subject or others [an AE], results in enrollment of an ineligible subject, causes subject to be withdrawn from study, prevents subject from being evaluable for the study's primary endpoint, results in enrollment of more than the approved number of subjects). Single example marked here as an illustration; this example or others may be applicable per DMC Study Charter.

Table 4. Subject status*

	Group A *N = XXX* *n (%)*	*Group B* *N = XXX* *n (%)*
Randomized	**xx**	**xx**
Received at least one dose of study treatment	**xx (xx)**	**xx (xx)**
Still on study treatment as of data cut	xx (xx)	xx (xx)
Completed study per protocol	xx (xx)	xx (xx)
Discontinued from study treatment early	xx (xx)	xx (xx)
Discontinued treatment but remains on study	xx (xx)	xx (xx)
Discontinued from both treatment and study	xx (xx)	xx (xx)
Reason for treatment discontinuation		
Adverse event	xx (xx)	xx (xx)
Lack of efficacy	xx (xx)	xx (xx)
Noncompliance	xx (xx)	xx (xx)
Etc.	xx (xx)	xx (xx)

*Depending on the rate of discontinuations, the DMC may consider adding a Kaplan-Meier plot of time to discontinuation by treatment group.

Table 5. Study treatment duration and dosage modifications*

	Group A *N=XXX*	*Group B* *N=XXX*
Weeks on treatment		
N	xx	xx
Mean (SD)	xx (xx)	xx (xx)
Range (min, max)	x, xx	x, xx
Quartiles (25th, median, 75th)	xx, xx, xx	xx, xx, xx
n (%) > 8 weeks	xx (xx)	xx (xx)
n (%) > 16 weeks	xx (xx)	xx (xx)
Subjects with any dosage modification (i.e., reduction or interruption)	xx (xx)	xx (xx)
Subjects with any dosage reduction	xx (xx)	xx (xx)
Only one reduction	xx (xx)	xx (xx)
Two or more reductions	xx (xx)	xx (xx)
Subjects with a reduction due to:	xx (xx)	xx (xx)
Adverse event	xx (xx)	xx (xx)
Other	xx (xx)	xx (xx)
Subjects with any dosage interruption	xx (xx)	xx (xx)
Only one interruption	xx (xx)	xx (xx)
Two or more interruptions	xx (xx)	xx (xx)
Subjects with an interruption due to:	xx (xx)	xx (xx)
Adverse event	xx (xx)	xx (xx)
Non-compliance	xx (xx)	xx (xx)
Other	xx (xx)	xx (xx)

* The summary of study treatment will depend on the specifics of the treatment (e.g., duration of therapy, allowable dosage modifications), but this provides a general framework for developing a summary that would be specific for a given study.

Table 6. Overview of adverse events

	Group A N=XXX		Group B N=XXX	
	n (%)[a]	# events[b] (rate)	n[a] (%)	# events[b] (rate)
Serious AE	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Related to blinded study treatment	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Grade 3+ AE	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Related to blinded study treatment	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
AE of special interest	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Related to blinded study treatment	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
AE resulting in modification of study treatment	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Related to blinded study treatment	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
AE resulting in discontinuation of study treatment	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Related to blinded study treatment	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Any AE	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Related to blinded study treatment	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)

a. Summarizes the number of participants with any event described in the row.

b. Summarizes the total number of events that occurred among subjects in the treatment arm.

Table 7. AEs by system organ class

	Group A N=XXX		Group B N=XXX	
Events, sorted alphabetically[a]	n (%)[b]	# events[c] (rate)	n[b] (%)	# events[c] (rate)
Any adverse event (AE)	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Blood and lymphatic system	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Cardiac	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Congenital and familial and genetic	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Ear and labyrinth	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Endocrine	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Eye	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Gastrointestinal	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
General and administration site conditions	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Hepatobiliary	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Infections and infestations	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Immune system	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Injuries	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Investigations	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Metabolism and nutrition	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Musculoskeletal	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Neoplasms	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Nervous system	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Perinatal conditions	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Psychiatric	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Renal and urinary	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Reproductive system	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Respiratory	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Skin	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Social circumstances	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Surgical and medical procedures	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Vascular	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)

a. Specify the sorting order/method here. Descending order is preferred but approach should be agreed upon a priori by the DMC and sponsor.

b. Summarizes the number of participants with any event described in the row.

c. Summarizes the total number of events that occurred among subjects in the treatment arm.

Table 8. Serious adverse events

MedDRA System Organ Class / High Level Term / Preferred Term	Group A N=XXX		Group B N=XXX	
	n (%)[a]	# events[b] (rate)	n[a] (%)	# events[b] (rate)
Any SAE	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Gastrointestinal disorders	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Abdominal pain	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Abdominal pain upper	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Abdominal pain lower	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Abdominal pain	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Nausea and vomiting	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Nausea	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Vomiting	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Etc.	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
SOC 2	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
HLT 1	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Preferred term 1	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Preferred term 2	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)
Etc.	xx (xx)	xx (x.x)	xx (xx)	xx (x.x)

a. Summarizes the number of participants with any event described in the row.

b. Summarizes the total number of events that occurred among subjects in the treatment arm.

*DMC may want to add/prioritize or perform sorting based on typical events monitored given the nature of the study.

Table 9. Summary of clinically significant laboratory abnormalities in follow-up*

	Group A *n (%)*	*Group B* *n (%)*
Hematology		
Hemoglobin	xx (xx)	xx (xx)
Platelet count	xx (xx)	xx (xx)
Absolute neutrophil count	xx (xx)	xx (xx)
White blood cell count	xx (xx)	xx (xx)
Activated partial thromboplastin time	xx (xx)	xx (xx)
Prothrombin time	xx (xx)	xx (xx)
Liver function		
Alanine amino transferase	xx (xx)	xx (xx)
Aspartate amino transferase	xx (xx)	xx (xx)
Total bilirubin	xx (xx)	xx (xx)
Alkaline phosphatase	xx (xx)	xx (xx)
Electrolytes		
Hypocalcemia	xx (xx)	xx (xx)
Hypercalcemia	xx (xx)	xx (xx)
Hypokalemia	xx (xx)	xx (xx)
Hyperkalemia	xx (xx)	xx (xx)
Hyponatremia	xx (xx)	xx (xx)
Hypernatremia	xx (xx)	xx (xx)
Chemistries		
Hypoglycemia	xx (xx)	xx (xx)
Hyperglycemia	xx (xx)	xx (xx)
Albumin	xx (xx)	xx (xx)
Creatinine	xx (xx)	xx (xx)

* A concise summary table of the lab parameters is only possible if the dataset contains indicators of clinical significance or toxicity grades for departures from normal. While often this is not the case, this is a potential option for summarizing the lab data that allows quick determination of any safety signal. Another option is to summarize the number of emergent above and below normal values or clinically significant high/low values.

Table 10. Liver enzyme elevations

	Group A *N=XXX* *n (%)*	*Group B* *N=XXX* *n (%)*
Hy's Law without cholestasis[a]	**xx (xx)**	**xx (xx)**
Hy's Law with cholestasis[b]	**xx (xx)**	**xx (xx)**
Highest ALT in follow-up		
< 2 × UNL	xx (xx)	xx (xx)
2 - < 3 × UNL	xx (xx)	xx (xx)
3 - < 5 × UNL	xx (xx)	xx (xx)
≥ 5 × UNL	xx (xx)	xx (xx)
Highest AST in follow-up		
< 2 × UNL	xx (xx)	xx (xx)
2 - < 3 × UNL	xx (xx)	xx (xx)
3 - < 5 × UNL	xx (xx)	xx (xx)
≥ 5 × UNL	xx (xx)	xx (xx)
Highest total bilirubin in follow-up		
≤ 2 × UNL	xx (xx)	xx (xx)
> 2 × UNL	xx (xx)	xx (xx)
Highest alkaline phosphatase in follow-up		
≤ 2 × UNL	xx (xx)	xx (xx)
> 2 × UNL	xx (xx)	xx (xx)

a Counts are subjects with 3-fold or greater elevations above the UNL of ALT or AST, elevations of serum total bilirubin greater than 2×UNL, and without elevations of alkaline phosphatase greater than 2×UNL.

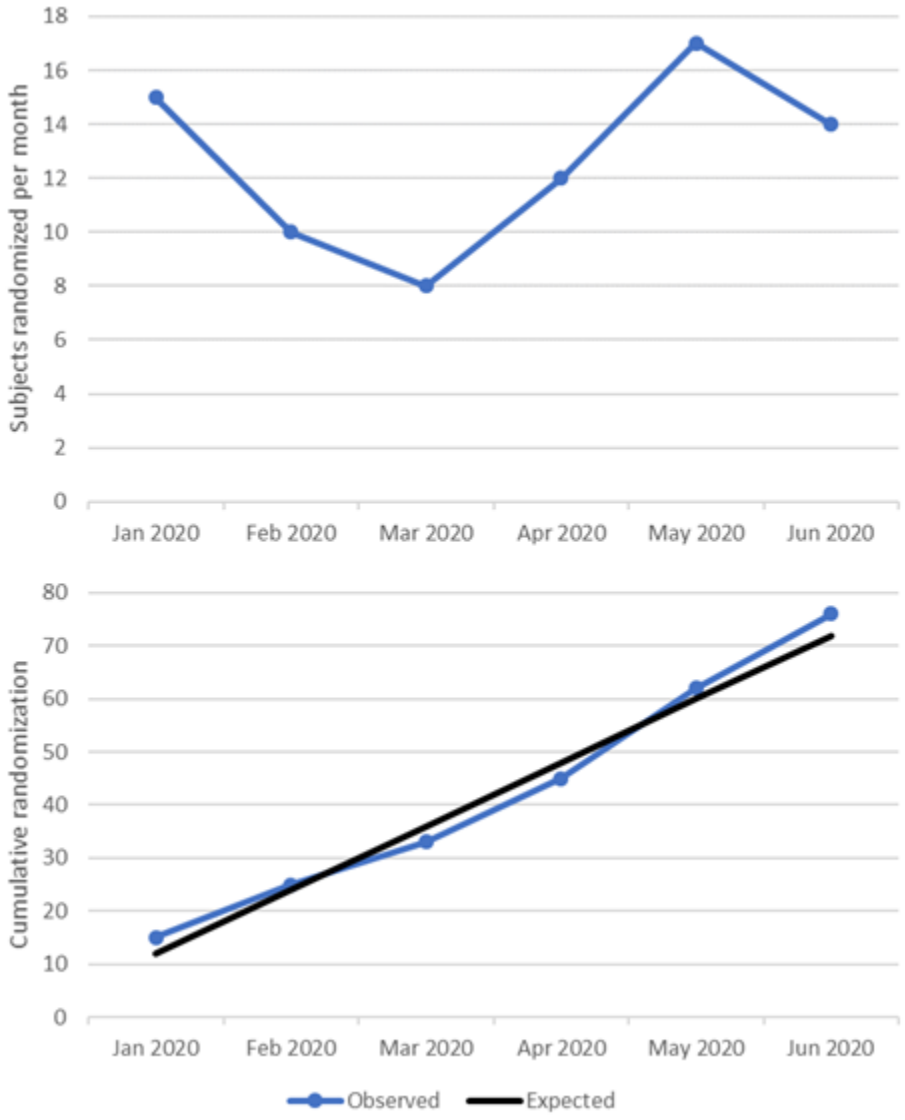
b Counts are subjects with 3-fold or greater elevations above the UNL of ALT or AST, elevations of serum total bilirubin greater than 2×UNL, and elevations of alkaline phosphatase greater than 2×UNL (initial findings of cholestasis).

Table 11. Summary of notable ECG changes from baseline

	Group A *n (%)*	*Group B* *n (%)*
QTcB		
Increase from baseline > 30 ms	xx (xx)	xx (xx)
Increase from baseline > 60 ms	xx (xx)	xx (xx)
Ever between > 450 to 480 ms	xx (xx)	xx (xx)
Ever between > 480 to 500 ms	xx (xx)	xx (xx)
Ever > 500 ms	xx (xx)	xx (xx)
QTcF		
Increase from baseline > 30 ms	xx (xx)	xx (xx)
Increase from baseline > 60 ms	xx (xx)	xx (xx)
Ever between > 450 to 480 ms	xx (xx)	xx (xx)
Ever between > 480 to 500 ms	xx (xx)	xx (xx)
Ever > 500 ms	xx (xx)	xx (xx)
HR		
> 25% decrease from baseline to < 50 bpm	xx (xx)	xx (xx)
> 25% increase from baseline to > 100 bpm	xx (xx)	xx (xx)
PR		
> 25% increase from baseline to > 200 ms	xx (xx)	xx (xx)
QRS		
> 25% increase from baseline to > 110 ms	xx (xx)	xx (xx)

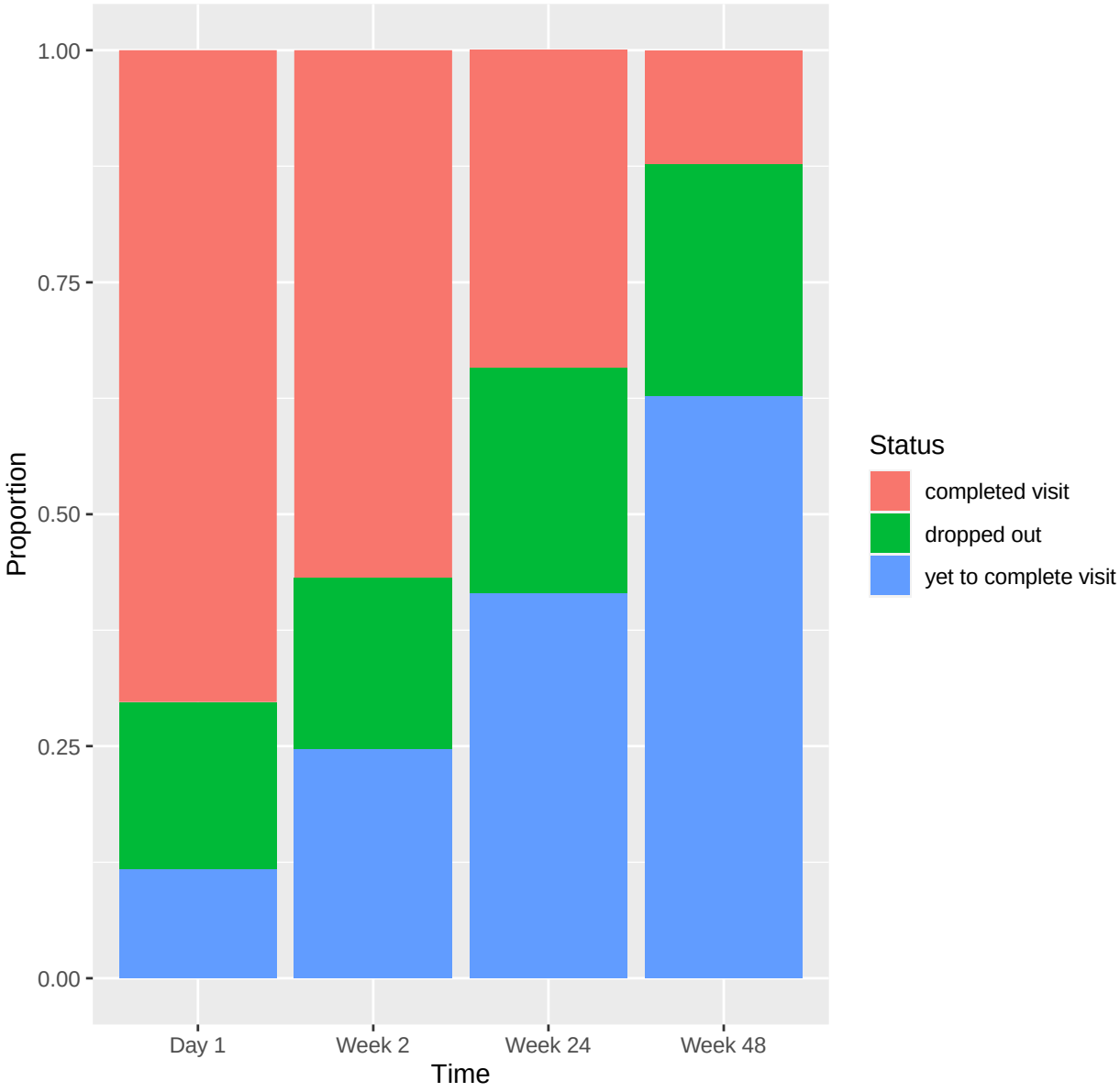
FIGURES

Figure 1. Actual and estimated randomizations by study month*



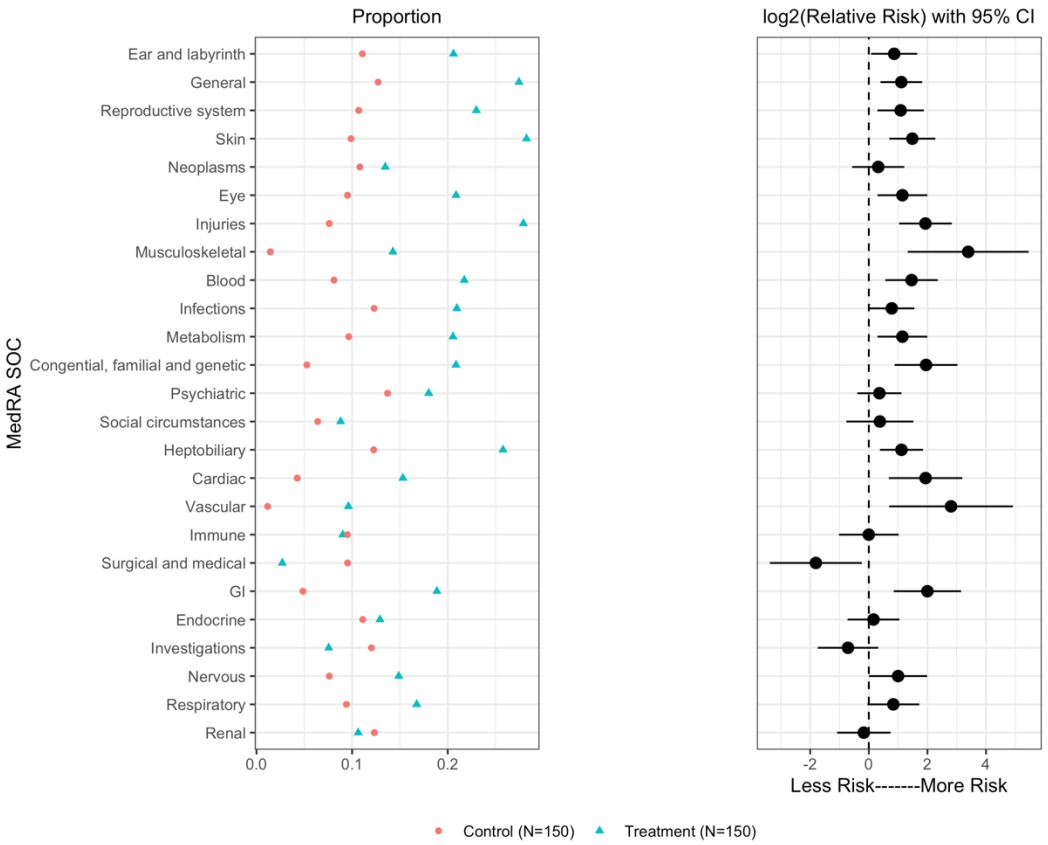
*This figure may be left out of the report if presented in the Sponsor's open session presentation of enrollment.

Figure 2. Compound bar chart of data availability by scheduled study visit*



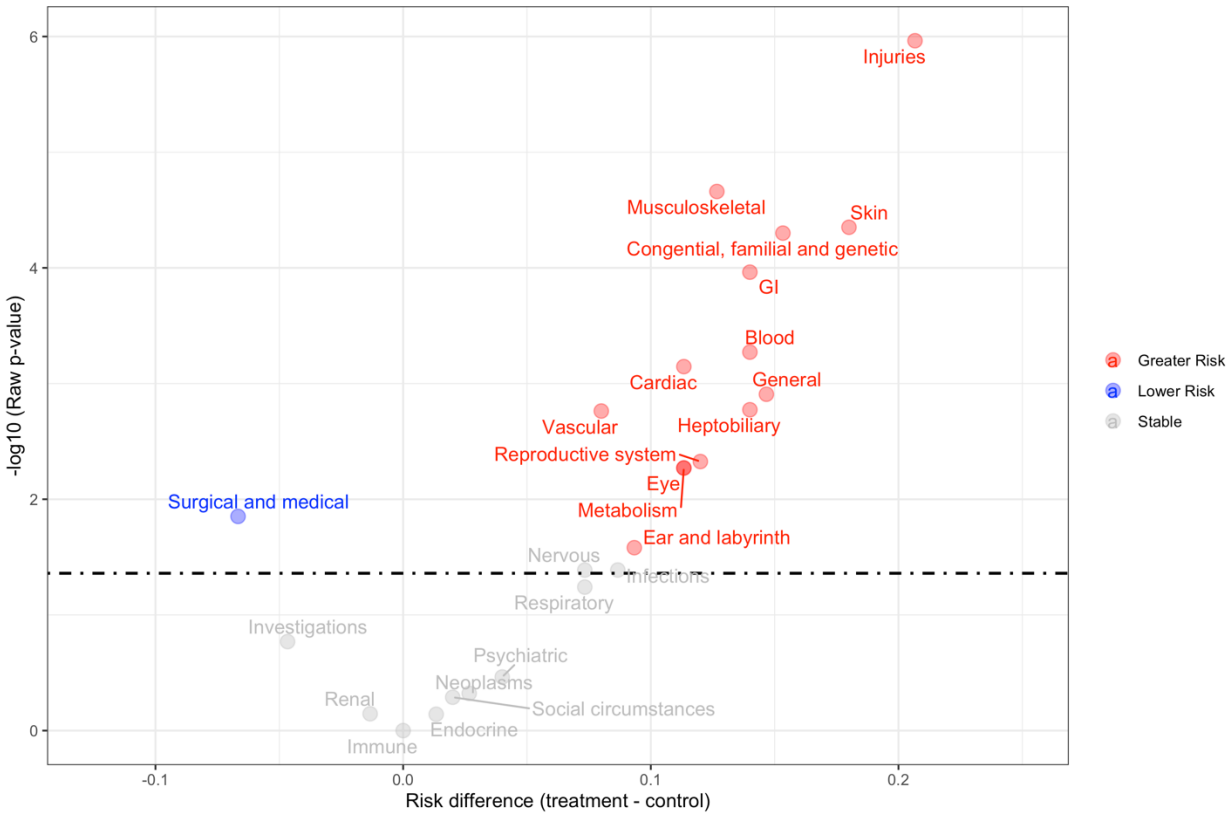
*The DMC may wish to have this presented separately by treatment arm, particularly if discontinuations from study are expected to differ by group. This plot categorizes enrolled participants at each visit as i) completed visit; ii) dropped out (missing because the participant discontinued from study); iii) yet to complete visit (missing and the participant is still on study).

Figure 3. AE dot plot and relative risk plot



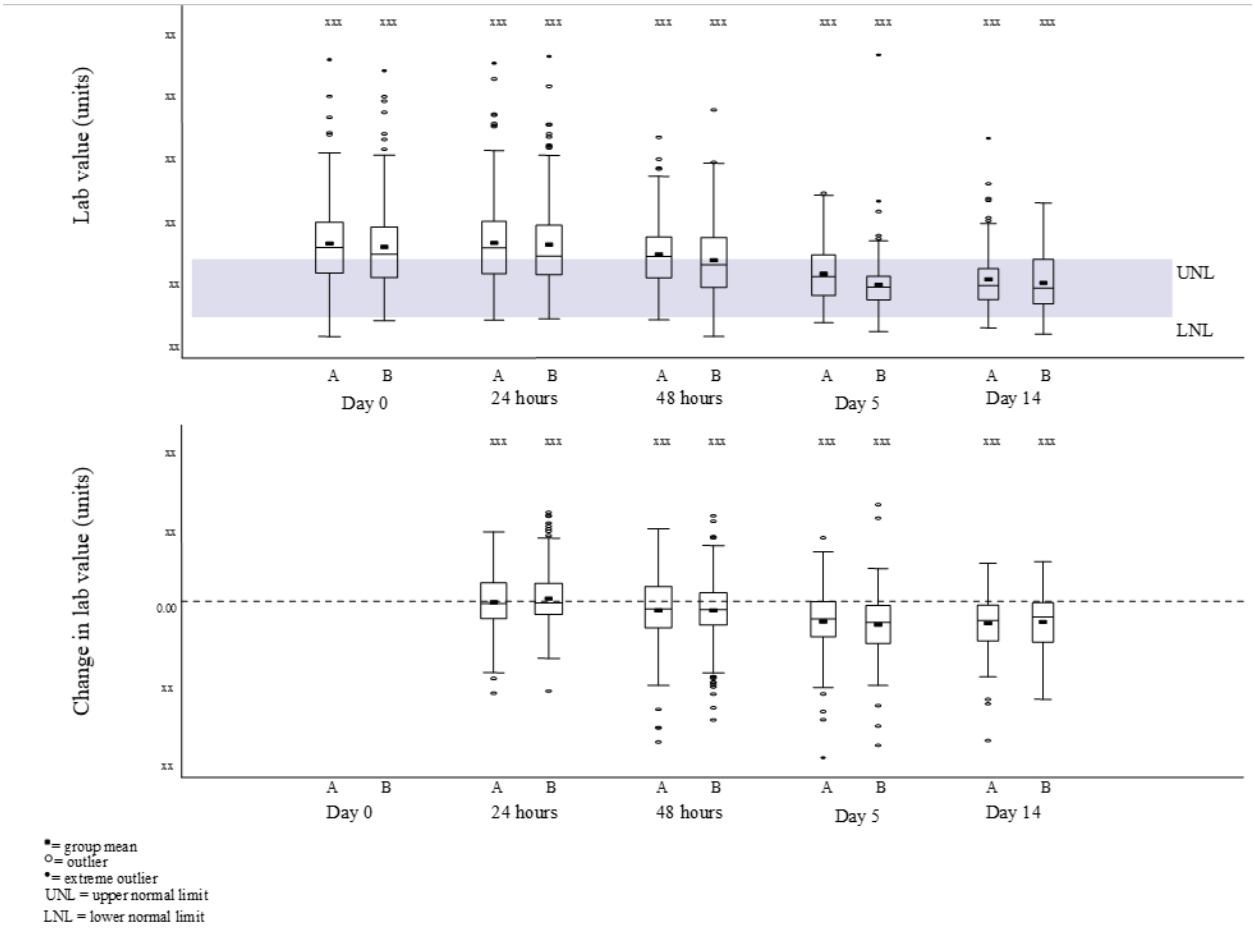
The left side of the figure shows % of patients exhibiting an AE in the treatment (triangle) or control (circle) groups. In the right side of the figure, 95% CIs for the log2(relative risk) that contain zero would be interpreted as showing no difference in risk between the two groups, while those contained completely within the region > 0 or < 0 would show increased risk for treatment or control, respectively. Every unit increase of the log2(relative risk) represents a doubling of the risk ratio between the treatments. Analyses by time intervals may further inform AE occurrence, e.g., proportion above could be replaced with rate (number of subjects with events divided by subject-years of follow-up) in the left plot, and risk difference (Treatment – Control) could be assessed in the right plot.

Figure 4. AE volcano plot



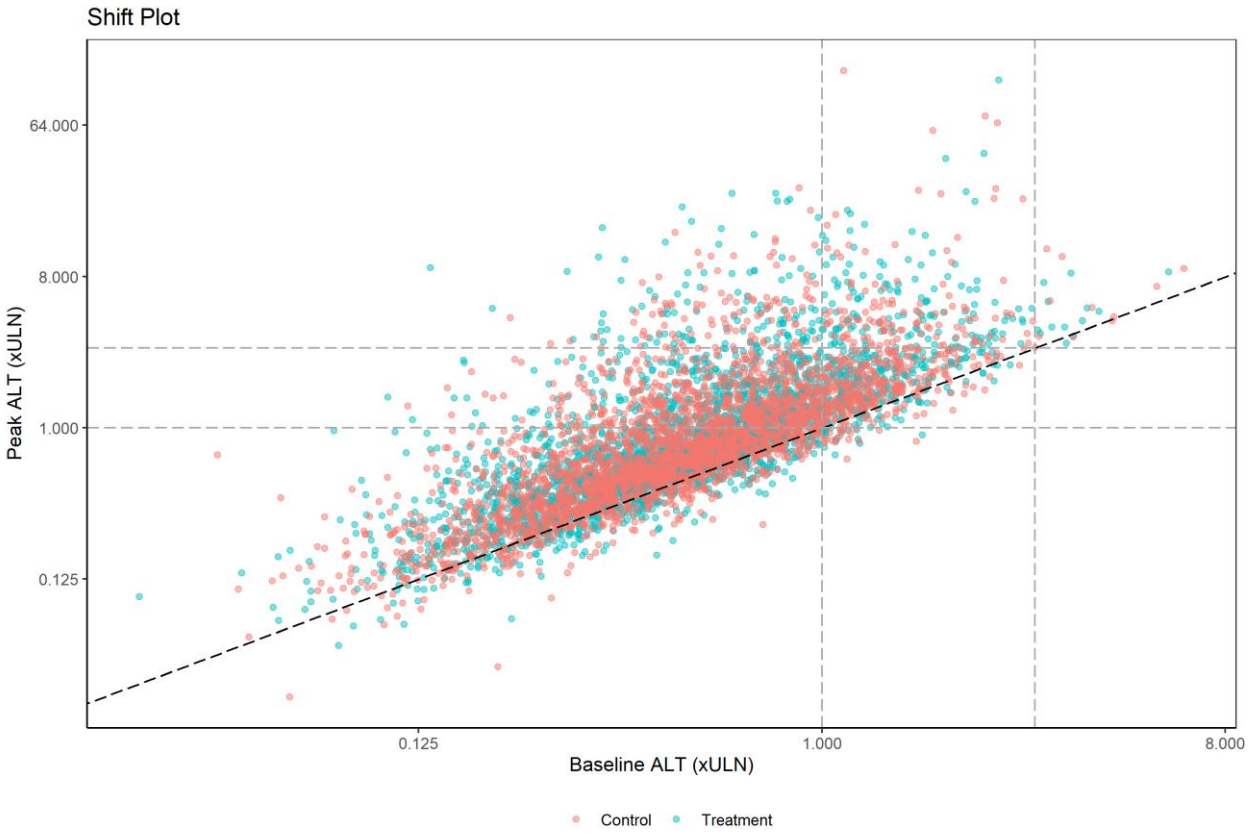
The x-axis represents the difference in proportions for each AE, and the y-axis represents the 2log10(raw p-value). The center of the circle denotes the coordinates for a particular AE. Red or blue implies greater risk for treatment or control, respectively. Events above the horizontal dot-dashed line are considered statistically significant when applying the false discovery rate multiplicity adjustment. Customization of the level at which this plot should be created should be based on events specific to anticipated AE issues or observed AEs as protocol proceeds.

Figure 5. Boxplots of laboratory values and changes over time*



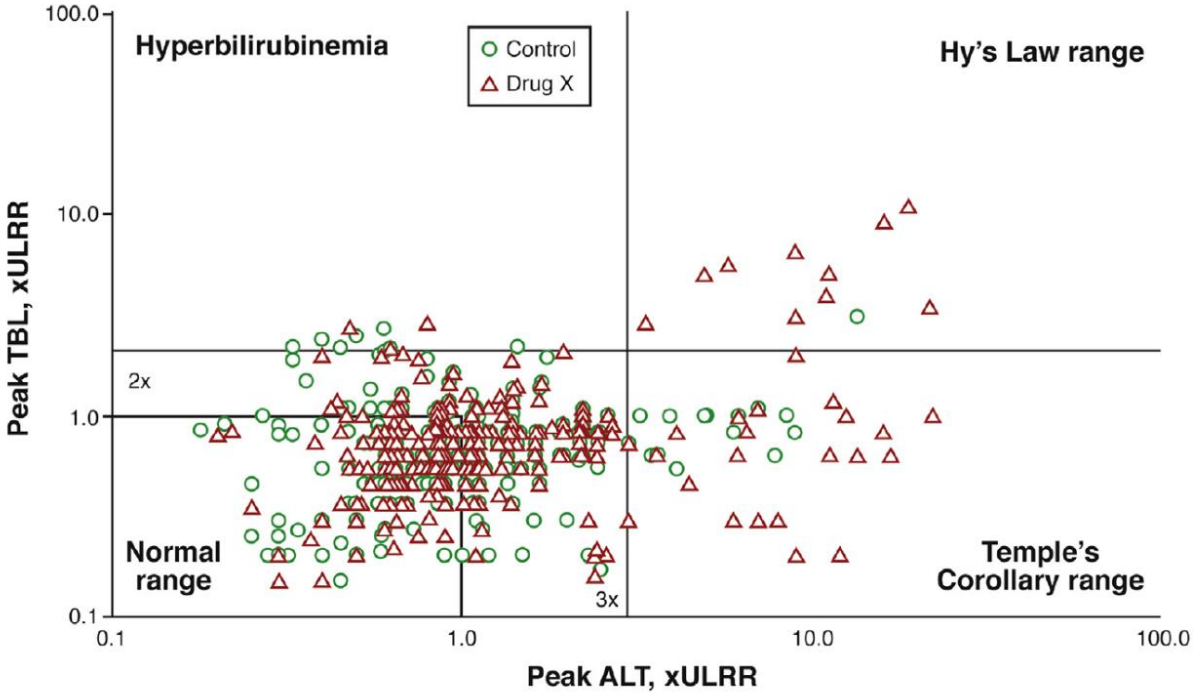
* Consideration should be given whether to plot the values and changes themselves (such as shown here), to present values relative to UNL (such as is often done for liver function tests), or log-transformed values (e.g., for highly skewed data). UNL and LNL cut-offs and use of separate graphs for subgroups, e.g., according to age categories or gender, should be decided a priori by DMC and the sponsor.

Figure 6. Shift plot of key laboratory data*



*Shifts from baseline are shown identifying treatment and control observations for peak versus baseline ALT (ULN refers to upper limit of normal). The plot indicates a greater shift in the treatment group, compared to controls. Out of range values can be color-coded or designated with grid marks as shown in this plot.

Figure 7. Hy's law graphic*



*Example taken from an editorial by Regev, A., and Bjornsson, E.S. (2014). "Drug-Induced Liver Injury: Morbidity, Mortality and Hy's Law." *Gastroenterology,* 147(1): 20-4.