# Innovative Use of Stacked Area Plots in DMC Reporting

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## INTRODUCTION

For many clinical trials, Data Monitoring Committees (DMCs) are charged with monitoring the safety of trial participants. As trials evolve, there may be important trends over time and potentially between treatment groups in subject disposition, dose level, adverse events (AEs), laboratory abnormalities, and other measures of interest.

**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 and/or changes over time, and to review a large amount of information in a short amount of time.

Among the graphical tools available, the *stacked area plot* can be particularly illuminating. A stacked *bar plot* may be used to display the distribution of ordered categorical data at a given point in time; when the number of time points is large, the individual bars become small, and the effect is a display of "stacked areas."

Stacked area plots provide a cross-sectional illustration of changes in "state" over time, where each subject's state can be known (at least in principle) throughout the time period of interest. Examples of states may include patient status, assigned dose of medication, intensity of an AE of interest, or level of a lab analyte.

## EXAMPLE 1: SUBJECT DISPOSITION

**Background.** We typically produce a set of two parallel reports, a Closed Session Report (DMC only) and an Open Session Report, which is used during the portion of the meeting that includes the trial sponsor and study leadership. One of the purposes of the Open Session is to discuss the disposition of trial subjects.

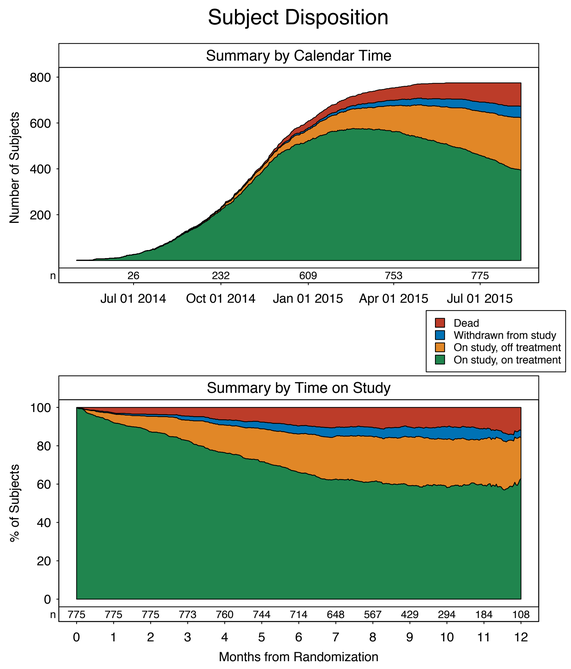
**Potential DMC Concerns.** In addition to reviewing the progress of enrollment over time, members of the DMC often focus on evaluating adherence to treatment and the extent to which subjects continue in follow-up for ascertainment of study endpoints.

**Standard Data Summaries.** Typical displays used to address these issues include a cumulative accrual plot, a table with the proportion of subjects who have discontinued treatment and/or follow-up, and a numeric summary of cumulative follow-up.

**Added Value of Stacked Area Plots**. Displays such as those presented in this example permit the integration of different types of information in a single plot, presenting a cross-sectional look at the study population over the course of both calendar time (top panel) and time from randomization (bottom panel).

**Data Collection and Restructuring.** The clinical information used to create the displays is a series of potential event dates for each subject: date of randomization, end-of-treatment date, end-of-study date, death date. If a given event hasn't been reported by the time of data transfer, the subject is assumed to be in the last known state.

The data are transformed into a structure with one record per subject-day (or date), coded with one of the following status categories: 0 = not yet randomized, 1 = on treatment, 2 = off treatment, still being followed, 3 = off-study, not known to be dead, or 4 = dead.




**Plotting Options.** In this display, subjects are aggregated across treatment group; separate plots for each treatment group could also be generated for the Closed Session Report. Also note that the y-axis for the top panel is *Number of Subjects,* allowing cumulative accrual to be read off the top; the bottom panel displays *Percent of Subjects.*

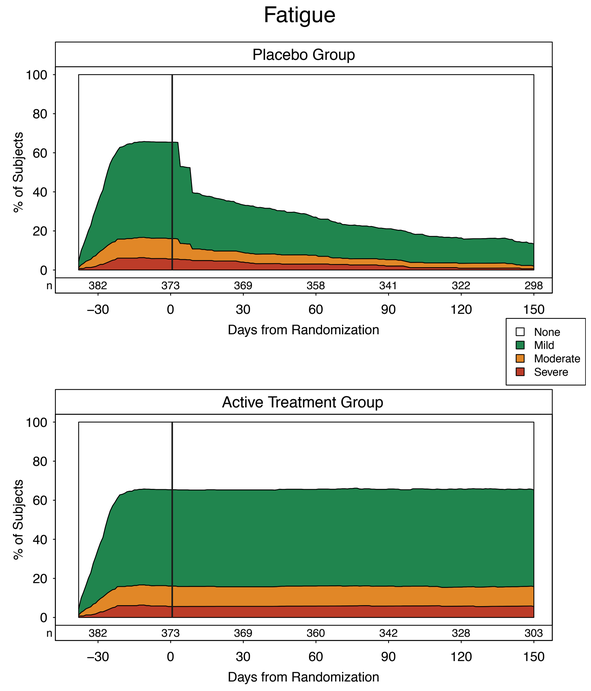
## EXAMPLE 3: ADVERSE EVENTS

**Clinical Setting**. This is a simulated example of a trial with a run-in period prior to randomization in which all subjects receive the active agent; those tolerating the drug are then randomized to either continue on active drug or switch to placebo. The DMC wants to be able to compare the two treatment groups with respect to key adverse events.

**Challenges in Summarizing Data.** Studies with multiple treatment phases with potential carryover effects of an active drug (and no washout period) present a challenge for analysis.

- Summaries of "treatment emergent" events, based only on events with onset dates on/after the start date of randomized treatment will *underestimate incidence in the active treatment group*, since AEs that represent ongoing states such as "fatigue" are likely to have begun prior to randomization.
- An alternate approach, including all AEs that either began after the start of randomized treatment or were ongoing at that time, may *overestimate incidence in the placebo group* if there are carryover effects.

**Visual Display of Adverse Event Burden**. A stacked area plot of AE intensity over time can illustrate the *burden* of the adverse effect by incorporating both duration and severity. Severity codes are assigned to each subject-day: 0 = none, 1 = mild, 2 = moderate, or 3 = severe. Events with no stop date are assumed to be ongoing through the date of data transfer.



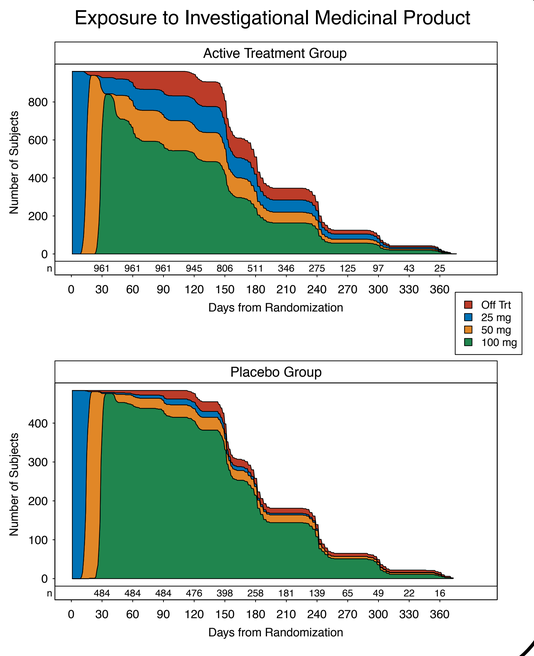

A cross-sectional display of subjects within each treatment group indicates whether the effect tended to carry over post-randomization and how long it took to resolve. Stacking by intensity permits the DMC to determine – for example – the proportion of subjects experiencing *moderate or worse* fatigue two months following the start of randomized treatment.

## EXAMPLE 2: DOSE TITRATION

**Clinical Setting.** This example represents a trial with a dose titration period spanning the first 6 weeks, allowing for up-titration at biweekly intervals until subjects reach their maximally tolerated dose. Follow-up visits are scheduled monthly through Month 6 and bimonthly thereafter. Dose reductions during the course of the trial are permitted based on tolerability.

**Potential DMC Concerns.** The DMC is interested in the pattern of dose titration, the dose levels achieved and maintained, as well as potential differences in adherence between treatment groups.

**Data Collection and Restructuring.** The IVRS system collects the actual date of each study visit, along with the dose level assigned at each visit; dates of treatment discontinuation are also collected. To create the stacked area plot, the data are transformed to include a record for each study day from randomization through the date of data cut-off or treatment termination, indicating the most recent dose level assigned.

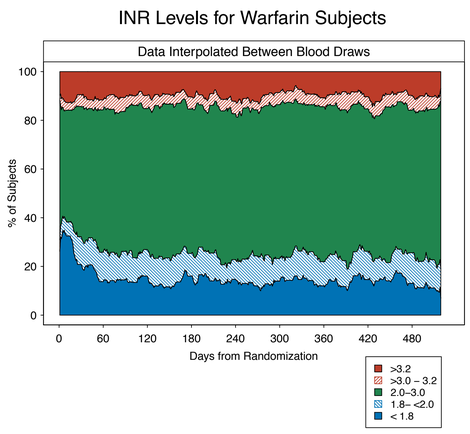



## EXAMPLE 4: LABORATORY MEASURES

**Clinical Setting.** This example represents a trial of Warfarin, an anticoagulant agent used to prevent stroke in subjects with atrial fibrillation. A surrogate marker of effect is the international normalized ratio (INR).

**DMC Concerns.** In order to monitor the safety of trial subjects, the DMC must evaluate how well the INR is being controlled; if the INR is too high, the subject is likely to experience bleeding; if INR is too low, treatment is likely to be ineffective. INR values between 2.0 and 3.0 are generally considered to be in the effective therapeutic range.

**Data Collection and Restructuring**. Blood samples are taken at frequent intervals to monitor INR. In order to create the stacked area plot, linear interpolation was done between blood draws for each subject, allowing the creation of a file with "daily" values. For the purpose of display, the continuous measure was divided into ranges of clinical interest representing "tight" control (INR 2.0 – 3.0) or "loose" control (INR 1.8 – 3.2).




## CONCLUSION

Stacked area plots provide an effective visual, cross-sectional summary of a study population over time, focusing on changes in state represented by ordered categories. While they are primarily *descriptive* in nature, they can reveal interesting patterns in the data that would not be captured using more focused analytic approaches. DMC members we have worked with have found them very useful in their deliberations.

For more information about SDAC, as well as a sample report, visit our website:

https://biostat.wisc.edu/content/clinical-trials-statistical-data-analysis-center-sdac