Clinical trial interim monitoring support: requirements and implementation
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Abstract
A clinical trial should never accrue a patient when the data collected to date indicate that this accrual could be unethical. An interim monitoring plan is a crude tool written into protocols to provide this assurance. At the University of Pittsburgh Cancer Institute, we have designed a software architecture to automate interim monitoring, acting appropriately when information required to determine whether a stopping criterion is fulfilled is missing. The design is modular and flexible.

Introduction
A clinical trials operation must strive for a zero tolerance of protocol violations. It must assure that no study can accrue past an interim monitoring time point if the protocol’s stopping rule states that accrual must be suspended. Nearly as important, the study should never be suspended unnecessarily; that is, if accruing an additional patient cannot lead to a stopping rule protocol violation, then the study should continue automatically. When the database is missing information required to determine whether a stopping criterion could be fulfilled, adequate warning must be given to stimulate data acquisition.

Interim monitoring algorithms
A small number of stopping rule monitoring algorithms are used in clinical trials at one institution. Each algorithm has two distinguishing components:

Component 1: Parameter set and forms
A data entry form for each algorithm is needed to hold the specific parameters needed to describe it. Example: For the Simon two-stage Phase II design[1], the parameters are:
- \( N_1 \) (first stage sample size for interim monitoring)
- \( R_1 \) (maximum # of patients with clinical response consistent with study termination at first stage)
For the Bryant-Day design [2], a third parameter is needed:
- \( T_1 \) (maximum # of toxicity-free patients consistent with study termination at first stage)
All algorithms also include a fairWarningBuffer parameter, discussed below, to address the fact that critical data are sometimes in arrears when needed.

Component 2: stoppingRuleHorizon() method
Inputs to stoppingRuleHorizon() consist of
- a) the current data for the particular clinical trial,
- b) the trial’s package of stopping rule parameters.
The return value is an integer representing (in essence) the minimum number of future patients that could be accrued and result in a protocol violation.
Example: For the Simon two-stage Phase II design, the dynamic inputs are \( n \)=current # of accrued patients who are or may turn out to be evaluable for response, \( r \)=current # of patients with clinical responses. Then stoppingRuleHorizon() returns \( N_1 - n + r - R_1 \).
For Bryant-Day, it returns (notation obvious) minimum(\( N_1 - n + r - R_1, N_1 - n + t - T_1 \)).
(When \( N_1 < n \) the full sample size is returned.)

Managing accrual suspensions and notifications
When a protocol is implemented, the monitoring algorithm is chosen and the parameters transcribed from the protocol document. When a dynamic input changes, stoppingRuleHorizon() is recomputed, and the following action table is scanned:

- If \( stoppingRuleHorizon() \leq 0 \), then set study status to “ACCRUAL SUSPENDED”
- If \( stoppingRuleHorizon() > 0 \), then set study status to “ACTIVE”
- If \( stoppingRuleHorizon() == fairWarningBuffer \), then dispatch e-mail warnings to update data.

Sometimes, it is certain that the stopping rule will be satisfied if the study continues. Our method correctly suspends accrual for “futility” even before \( n = N_1 \).

Conclusion
We believe that this architecture will facilitate rapid implementation of new interim monitoring algorithms, in automated mode that will patients are protected from inadequate response or excessive toxicity by assuring that the interim monitoring plan is followed.

References