Basel Biometric Section of the Austro-Swiss Region of the International Biometric Society

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BBS Seminar on Operational and Implementation Considerations in Adaptive Designs

Basel, 26 Oct 2009, 16:00 – 17:30

Basel, Auditorium of the Roche Learning Center, Aeschenvorstadt 56, Basel

PROGRAM

16:00 **Welcome** Michael Branson, President BBS

16:00 - 16:45 Eva Miller, PhD (ICON Clinical Research, US)

Logistical Considerations in the Implementation of Adaptive Trial Designs

Abstract

We will share actual experiences with the design and conduct of several clinical trials utilizing adaptive designs; these studies are ongoing or have been recently completed. Planning, teamwork, roles and responsibilities of team members, working with several data sources, possible data lag, preparing for DMCs, minimizing opportunities for bias, and managing randomization and drug supplies all cause logistical challenges. The importance of obtaining clean data rapidly is critical for the implementation of these designs. We will explore several successful studies, how the hurdles were tackled and what gains resulted.

(*extended abstract appends this notice*)

16:45 - 17:30 Norbert Benda, PhD (Novartis Pharma AG, Basel)

Considerations and Experiences in Adaptive Dose Finding

Abstract

Adaptive trials in the mid-phase of drug development offer a wide range of possibilities and challenges differing considerably from those in late phase development with respect to several analytical and procedural aspects. In contrast to confirmatory statements Phase II adaptive dose finding studies focus more on prediction, estimation and reassurance to the sponsor to go forward to Phase III. Achieving these mid-phase drug development goals requires techniques and procedural mechanisms that are different from those used in a confirmatory trial. The presentation provides a discussion of recent experiences and reflections on the chances, challenges and risks related to adaptive dose finding trials.

17:30 End of Seminar

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Extended abstract

Logistical Considerations in the Implementation of Adaptive Trial Designs (E. Miller)

Logistical and operational considerations in designing and implementing adaptive designs have recently drawn greater attention because the infrastructure for managing traditional double-blind, randomized, parallel group clinical trial does not lend itself to the challenges presented in implementation of flexible designs. The CHMP defined a trial as "adaptive" if statistical methodology allows the modification of a design element (e.g. sample-size, randomization ratio, number of treatment arms) at an interim analysis with full control of type I error. The benefits of employing adaptive designs include acceleration of the clinical trial process, enhancement of trial efficiency, and improvements in patient safety. To achieve these benefits clinical teams must adhere to the scientific method by incorporating plans for change in the study protocol and they must implement those planned changes efficiently and effectively. Adaptive designs may have one or more of the following rules applied to the interim look at data: (1) allocation rule, (2) sampling rule, (3) stopping rule, and/or (4) decision rule. Adaptive trial designs require more teamwork and planning before the study starts and different business models for implementation and managing the logistics of the trial than traditional designs. Some of the challenges which need to be dealt with relate to: (1) Planning interim efficacy evaluations with potential early stopping decision or trial extension based on established benefits and managing the actions required after interpretation of results; (2) The possibility of adding or shutting down treatment arms while the study is in progress based upon predetermined rules and how that will impact drug supply management and be handled without compromising study integrity; (3) Changing the ratio of subjects to treatment group or changing drug cohorts, again greatly impacting drug supply management; and (4) Adaptive randomization algorithms for maximizing balance of subject allocation requiring clear delineation of the algorithm and an IVR System custom built and validated for the specific randomization algorithm. Particular statistical challenges are encountered with each type of adaptive design and designs combining several forms. For example, dose escalation studies may have a variety of experimental designs to best suit particular therapeutic areas and experimental problems. Study design and practical implications of several case studies will be described in detail.