

Thursday 25 July 2024

09:00-12:30 Mini Symposium 1 (Room 1)

Beyond conventional RCTs: Exploring design options and modeling in drug development

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Regulatory aspects

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The confirmatory nature of the evidence generated to answer the primary research question of efficacy for new drugs is a cornerstone in regulatory decision making. The randomised clinical trial – in many of its shapes and forms – is the proven successful design to address this. Regulatory perspectives on novel design options and modelling approaches typically would, and possibly should, start from this proven quality of the RCT. Regulatory approval and subsequent reimbursement decisions are of huge importance to large populations of patients and have large societal impact. Ensuring a high standard of (confirmatory) evidence for such decision making is thus a shared obligation across all stakeholders involved. At the same time: (1) the RCT as often employed has known limitations in some settings, (2) decision making involves assessing a totality of evidence for benefit – risk and overall drug characteristics and (3) advancement of science and in-depth knowledge of disease (from molecule to man) and methodology & modelling have the potential for improving research designs for the (broad) range of research questions relevant for drug development. In specific settings such as rare diseases and pediatric development and novel treatment modalities (e.g. anti-sense oligo nucleotides almost tailored to individual patients) the classical confirmatory RCT may not be possible or will actually not be able to answer the primary research questions within a reasonable time frame. Modelling underpinning research design, data collection and analysis is in some sense at the very core of statistics (following Sir D.R. Cox): statistical inference is at its core based on an assumed model for the data generating mechanism. The usual (regulatory) statistical standards for assessing the level of evidence for confirmatory trials (type 1 error control, power, p-values etc.) may not be sufficient to establish the strength of (confirmatory) evidence of more complex designs, of results that substantially build on modelling results with limited data, or real world data studies. For modeling and simulation (complex) models, a credibility framework was proposed, that takes a broader perspective, specifically including the considerations of the size of impact and risk on the regulatory decision. In this presentation, regulatory aspects for typical examples - inspired by the presentations in this session - will be discussed based on the broader context of regulatory decision making and the principles underlying such a credibility framework.