2025 年第 1 回計量生物学講演会

Challenges in the design and analysis of clinical trials

– with a special focus on values below a lower limit of quantification and (adaptive) group sequential trial designs

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16th May, 2025 (Fri) チュートリアル終了後

富山国際会議場　多目的会議室 201-202（富山県富山市大手町１－２）

共催：日本計量生物学会

北海道大学医学部医学統計学教室

京都大学大学院医学研究科社会健康医学系専攻臨床統計家育成コース

Challenges in the design and analysis of clinical trials – with a special focus on values below a lower limit of quantification and (adaptive) group sequential trial designs

Randomized clinical trials are seen as the gold standard in clinical research when it comes to evidence regarding the effectiveness and safety of a new treatment. A plethora of statistical methodology is available for addressing different types of clinical study design and analysis. However, many open research questions remain. In this talk, we will discuss new research results that deal with addressing values below a lower limit of quantification (LLOQ), as they often arise in pharmacokinetic clinical trials. Secondly, this talk will include a discussion of statistical issues related to (adaptive) group sequential clinical trial designs, often faced in phase 3 trials.

In pharmacokinetic trials, usually in a dose escalation setting, measurements of drug concentrations may be below a specific threshold due to technical detection limits. In such cases, we only know that the value lies between zero and a specific threshold. Such measurements are referred to as values below the lower limit of quantification. One frequently applied solution is the imputation of those measurements by one half of the threshold, i.e. LLOQ/2. However, other solution strategies also exist. Some are also based on imputing a given value, while others are rather model-based, e.g. the tobit model. In the literature, the focus is often on descriptive or simple testing settings rather than multivariable regression modelling. In the setting of multivariable regression modelling, we ran a systematic simulation study comparing different statistical methods. We discuss the relevance of the results for the application of multivariable regression modelling with LLOQ variables.

The second part of the talk deals with (adaptive) group sequential clinical trial designs and related challenges. Group sequential trial designs allow for an early stopping of the trial and a stage-wise inclusion of new patients. Adaptive group trials also allow for adapting the design of the study while the study is ongoing. A frequent assumption in both study types is that outcomes are immediately observed at the interim analysis. However, questions arise when this assumption does not hold: What happens if delayed responses are not accounted for in the trial design and how large is the gain of applying modified trial designs in such cases? We will discuss our findings from an extensive simulation study addressing those questions [1].
A point of criticism regarding (adaptive) group sequential trial designs is the unblinding at the interim analysis. Blinded interim analyses are preferred by the medical evaluation agencies. However, aiming for an early trial stop or the adaptation of the guessed effect size influencing a sample size recalculation, can only be addressed by designs with an unblinded interim analysis. Hence, we introduced a new hybrid trial design. We focus on trials with a time-to-event endpoint, which usually take a long time. The hybrid approach means that depending on the overall event number at the blinded interim analysis, a decision is made whether to unblind the analysis with a potential early trial stop or trial adaptations, or whether to continue blinded as originally planned. We compare three different variants of this new trial design and discuss their design properties based on a thorough simulation study.

Literature:
[1] Schüürhuis, S., Wassmer, G., Kieser, M., Pahlke, F., Kunz, C. U., & Herrmann, C. (2024). Two-stage group-sequential designs with delayed responses–what is the point of applying corresponding methods?. *BMC Medical Research Methodology*, *24*(1), 242.

1. 概要

日時：2025 年 5 月 16 日(金) 日本計量生物学会・応用統計学会チュートリアル終了後
開催形式：ハイブリッド開催(現地・ZoomWebinar)
現地会場：富山国際会議場　多目的会議室　201-202
〒930-0084 富山県富山市大手町 1 － 2
https://www.ticc.co.jp/
参加登録方法：日本計量生物学会年会もしくはチュートリアル参加者は不要です．日本計量生物学会会員かつ，年会にもチュートリアルにも不参加の場合，事務局へ参加申し込みメールをご送信ください（期限：2025 年 5 月 14 日）
Peatix サイトアドレス：https://biometricsseminar202505.peatix.com/
参加費：会員，日本計量生物学会年会，応用統計学会年会，チュートリアル参加者無料
定員：現地参加 150 名，オンライン参加 500 名（年会・チュートリアル参加者優先、会員先着順）

2. 当日の参加方法

現地参加の方は，年会・チュートリアルの名札を下げて入室してください．オンライン参加の方は，メールにて配信された Zoom の URL から入室してください．なお，本セミナーはオンラインでリアルタイムに配信しますが，オンデマンド(録画)配信は予定しておりません．

3. 試験統計家認定更新のための単位認定と参加証発行

試験統計家認定の更新を申請される方は，有効期間内に 30 単位を取得する必要があります．本講演会は“2 単位”となっており，1/15 を満たします．単位認定をご希望の現地参加の方は，参加受付時に出席確認をし，単位認定の受講証をお渡し致します．単位認定をご希望のオンライン参加の方は，当日に Zoom のチャット機能を利用して，そこに提示した URL のサイトで必要事項を記入いただくことで出席確認を行います．後日，出席確認された方に受講証をメールでお送りします．また，出席者には試験統計家認定とは別に参加証を発行します．

4. 問い合わせ先

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以上