Bayesian dose-escalation clinical trial

A Bayesian dose-escalation clinical trial is a type of clinical trial design that incorporates Bayesian statistical methods to guide the decision-making process during the dose-escalation phase. Dose-escalation trials are commonly conducted in early-phase clinical trials, especially in the field of oncology, to determine the maximum tolerated dose (MTD) of a new experimental drug.

Here's a brief overview of key concepts related to Bayesian dose-escalation clinical trials:

Dose-Escalation.

Bayesian Statistics: Bayesian statistics is a branch of statistics that involves updating probabilities based on new evidence. In the context of clinical trials, Bayesian methods allow for the incorporation of prior information (prior beliefs) and the continuous updating of beliefs as new data becomes available.

Bayesian Dose-Finding Designs: Bayesian dose-escalation designs use statistical models to estimate the probability of toxicity or efficacy at different dose levels. These models integrate both prior information and observed data to make informed decisions about dose escalation, de-escalation, or stopping the trial.

Adaptive Design: Bayesian dose-escalation trials often use adaptive designs, allowing the trial to be modified based on interim data analysis. This adaptability enables researchers to efficiently explore the dose-response relationship and make informed decisions about dose adjustments during the trial.

Decision Criteria: Bayesian methods help define decision criteria for dose escalation, such as the probability of exceeding a certain level of toxicity or achieving a desired level of efficacy. These criteria are typically defined in advance based on a balance between safety and efficacy considerations.

Small Sample Sizes: Bayesian approaches can be particularly useful in situations where the sample size is relatively small, as they allow for the incorporation of prior knowledge to supplement limited data.

By using Bayesian methods in dose-escalation trials, researchers aim to optimize the efficiency of the trial process, identify the MTD more quickly, and minimize the number of patients exposed to suboptimal or toxic doses. However, the choice between Bayesian and frequentist approaches depends on various factors, and both methods have their strengths and limitations. Regulatory agencies, such as the U.S. Food and Drug Administration (FDA), may have specific guidance on the design and analysis of clinical trials. Researchers and statisticians should carefully consider the appropriateness of Bayesian methods for their specific study objectives.

Cox et al. performed a randomized, double-blind, placebo-sham-controlled Bayesian dose-escalation clinical trial at 2 children's hospitals in Houston, TX, and Phoenix, AZ, USA (NCT01851083). Patients 5-17 years of age with severe traumatic brain injury (Glasgow Coma Scale ≤ 8) were randomized to BMMNC or placebo (3:2). Bone marrow harvest, cell isolation, and infusion were completed by 48 hours post-injury. Bayesian continuous reassessment method was used with cohorts of size 3 in the BMMNC group to choose the safest between 2 doses. Primary endpoints were quantitative brain

volumes using magnetic resonance imaging and microstructural integrity of the corpus callosum (CC; diffusivity and edema measurements) at 6 months and 12 months. Long-term functional outcomes and ventilator days, intracranial pressure monitoring days, intensive care unit days, and therapeutic intensity measures were compared between groups. Forty-seven patients were randomized, with 37 completing 1-year follow-up (23 BMMNC, 14 placebo). BMMNC treatment was associated with an almost 3-day (23%) reduction in ventilator days, 1-day (16%) reduction in intracranial pressure monitoring, and 3-day (14%) reduction in intensive care unit (ICU) days. White matter volume at 1 year in the BMMNC group was significantly preserved compared to placebo (decrease of 19891 vs 40491, respectively; mean difference of -20600, 95% CI: -35868 to -5332; P = 0.01), and the number of CC streamlines was reduced more in placebo than BMMNC, supporting evidence of preserved CC connectivity in the treated groups (-431 streamlines placebo vs. -37 streamlines BMMNC; mean difference of -394, 95% CI: -803 to 15; P = 0.055), but this did not reach statistical significance due to high variability. We conclude that autologous BMMNC infusion in children within 48 hours after severe traumatic brain injury is safe and feasible. The data show that BMMNC infusion led to 1) shorter intensive care duration and decreased ICU intensity; 2) white matter structural preservation; and 3) enhanced CC connectivity and improved microstructural metrics [1)].

1)
Cox CS Jr, Notrica DM, Juranek J, Miller JH, Triolo F, Kosmach S, Savitz SI, Adelson PD, Pedroza C, Olson SD, Scott MC, Kumar A, Aertker BM, Caplan HW, Jackson ML, Gill BS, Hetz RA, Lavoie MS, Ewing-Cobbs L. Autologous bone marrow mononuclear cells to treat severe traumatic brain injury in children. Brain. 2024 Jan 5:awae005. doi: 10.1093/brain/awae005. Epub ahead of print. PMID: 38181433.