Comparison of hierarchical EMAX and NDLM models in dose-response for early phase clinical trials

CURRENT STATUS: UNDER REVIEW

BMC Medical Research Methodology BMC Series

Byron Gajewski
University of Kansas Medical Center
bgajewski@kumc.edu*Corresponding Author*

Xiaqing Huang
University of Kansas Medical Center

DOI:
10.21203/rs.2.20244/v1

SUBJECT AREAS
Health Economics & Outcomes Research

KEYWORDS
Dosing design, Bayesian models, hierarchical EMAX, logistic, NDLM

Abstract

Phase II clinical trials are primarily aimed to find the optimal dose and investigate the relation between dose and efficacy relative to standard of care (control). Therefore, before moving forward to phase III confirmatory trial, the most effective dose is needed to be identified. The primary endpoint of phase II trial is typically a binary endpoint of success or failure. The EMAX model, ubiquitous in pharmacology research, was fit for many compounds and described the data well, except for a single compound, which had nonmonotone dose–response (Thomas et al., 2014). To mitigate the risk of nonmonotone dose response one of the alternative options is Bayesian hierarchical EMAX model (Gajewski et al., 2019). The hierarchical EMAX is a Proteus dose-response model, it adapts to its environment. When dose-response is monotonic it enjoys efficiency of EMAX. When dose-response is non-monotonic the additional random effect hyperprior makes the hierarchical EMAX model more adjustable and flexible. However, the normal dynamic linear model (NDLM) is a useful model to explore dose-response relation in that the efficacy at the current dose depends on the efficacy of the previous dose(s). Previous research has compared the EMAX to the hierarchical EMAX (Gajewski et al., 2019) and the EMAX to the NDLM (Liu et al., 2017), however, the hierarchical EMAX has not been directly compared to the NDLM. The focus of this paper is to compare these models and discuss the relative merit for each of their uses for an ongoing early phase dose selection study.

Full-text

Due to technical limitations, full-text HTML conversion of this manuscript could not be completed. However, the manuscript can be downloaded and accessed as a PDF.