

**TITLE: Design and analysis of clinical trials using Bayesian non-parametrics – application to single arm dose escalation studies**

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**ABSTRACT:** Dose escalation is a key component of early phase clinical development, as a basis for further dose optimisation in the target patient population either as monotherapy or in combination. Statistical methods guiding dose escalation are well developed, encompassing from robust designs based on lean distributional assumptions through to fully Bayesian regression approaches. A key point of differentiation here is the extent to which information is or is not borrowed across doses. For instance, in oncology regression approaches typically adopting monotonicity of the dose-response relationship have been amply replaced by more robust methods along the last decade or so, due to a concern that parametric regression assumptions may not appropriately reflect the underlying mechanism of action. This shift is not entirely cost-free, as reverting to more robust methods can result in less precise inferences and inflated sample sizes. To address this gap, a hierarchical regression approach using binary endpoints is presented here based on well-established methods for Bayesian non-parametric inference. The distinctive feature of this method is that a single coefficient ensures inferences against violation of monotonicity of the dose-response relationship. This method is applied to design of dose escalation studies in oncology settings where monotonicity may not hold are illustrated, such as the clinical development of T-cell engagers where excessive doses can lead to decreasing efficacy due to exhaustion of effector cells. Operational characteristics are contrasted with state-of-the-art methods, including scenarios where monotone non-linear regression performs well and scenarios where information borrowing across doses is not appropriate.