An ISoP Position Statement on the use of Dose-Exposure-Response in Drug Development

Herein, exposure refers to either actual or integrated drug concentrations in plasma (e.g., average concentration at steady state (Css)). The definition of exposure includes the site and type of measurement (blood, plasma, unbound, serum etc.) as well as model based concentrations. Response refers to clinical endpoints of benefits or risks, or biomarkers thereof, or both. The term 'Population-average Dose-Exposure-Response (D-E-R)' corresponds to what the pharmacometrics literature calls more formally the mean response curve [1] in the patient population.

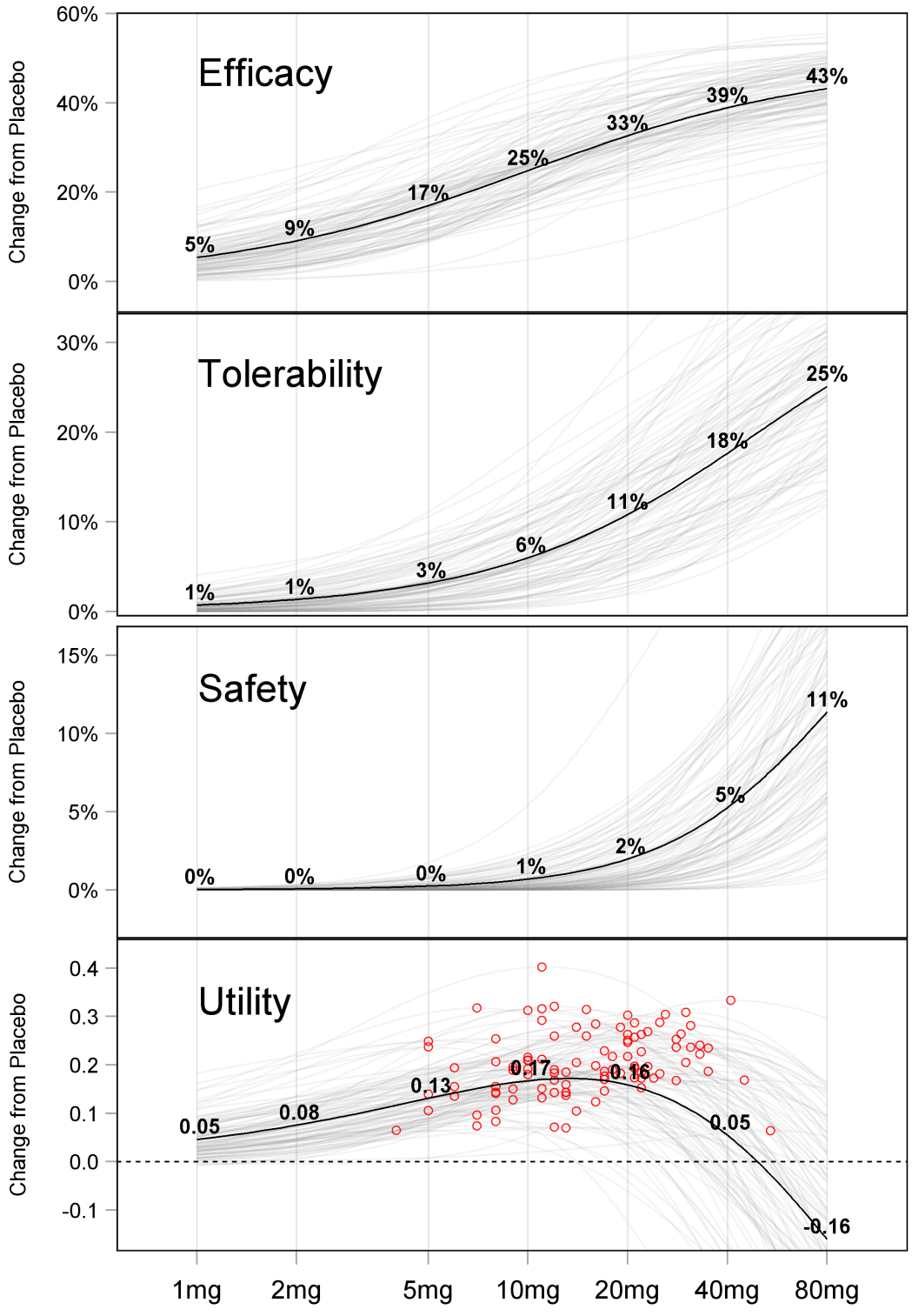
D-E-R should be at the centre of drug development and regulatory approval. As Lewis Sheiner [2] wrote "...the intellectual focus for clinical drug development should be on understanding (i.e., science and learning)" and this is best addressed through D-E-R analyses, for both benefits and risks. It is also the methodological underpinning for understanding what Morgan et al [3] have called the "three pillars of [Phase II] survival", namely exposure at the target site, target engagement, and expression of downstream pharmacology, which determine the fate of a drug in development.

To aid discussion, the specific definitions and roles of population-average D-E-R and individual D-E-R are described below, and illustrated in Figure 1.

- **Population-average D-E-R** typically describes the relationship between both benefits and risks to a **single** (patient level) summary measure of exposure from a **fixed** dosing regimen (e.g. Css). Well-conducted population-average D-E-R provides a clear evidence base to describe how both benefits and risks change as a function of these fixed dose regimens. This is critical for recommending the range of dose sizes that can be made available to patients. Importantly, population-average D-E-R relationships do not tell us the underlying D-E-R relationships for individual patients.

- **Individual D-E-R** typically describes the relationship between both benefits and risks to **multiple** individual patient measures of exposure from a **fixed and/or flexible** dosing regimen. With suitable designs, this will allow quantification of inter-individual variability (IIV) in D-E-R. Individual D-E-R relationships cannot be directly measured for all endpoints (e.g. the risk of a serious bleed with an anticoagulant). Where individual D-E-R relationships can be measured (e.g. renal function and T-cell populations as safety and efficacy measures during treatment with immunosuppressive drugs) these can and should be used to identify and improve adaptive dose individualisation algorithms.

Figure 1 The Population-average D-E-R relationship (bold line) and 100 individual D-E-R relationships (gray lines) for a notional Efficacy, Tolerability and Safety endpoint for a hypothetical drug. The Population-average D-E-R is simply the mean of the individual D-E-R relationships. The final panel (Utility) shows a very simple clinical utility index, where 'Utility score = Efficacy – Tolerability – 3*Safety' (e.g. the relative weighting is 1:1:3 for the three endpoints). The last panel highlights the maxima of the individual utility curves (red circles), showing that they are widely distributed over the dose range. No one dose is optimal for all patients.



Population-average D-E-R

Background

- Population-average D-E-R analyses are widely and successfully employed to quantify both benefits and risks, and provide the best and most coherent evidence base to evaluate fixed dose regimens. Pharmaceutical companies consistently use these analyses for internal decision-making.

- Using population-average D-E-R models, interpolation across the range of exposures studied is clearly understood, and universally agreed as scientifically sound.

- The traditional focus on very limited dose ranges in Phase 3 is the primary limitation in these analyses. The resulting exposure ranges are far too condensed and narrow, weakening the precision and usefulness of the results.

Key Recommendations

- To enable accurate and precise population-average D-E-R results, very wide dose ranges (such as those historically used in phase 2) should be employed **throughout** drug development. That is, all late phase studies should be optimally designed to support these integrated analyses. Both sponsors and regulators can then evaluate the results across this wide dose range to recommend the range of doses sizes to make available to patients. In the absence of knowledge of individual D-E-R relationships, the availability of such dose ranges is important so that patients may cautiously titrate to optimize benefit/risk at the individual patient level.

- To encourage regulators to identify population-average D-E-R analyses for both benefits and risks as a central tool for the evaluation of new drugs [4], and to consider well-conducted D-E-R analyses as superior scientific evidence compared with two studies with '$p<0.05$'.

Individual D-E-R

Background

- Woodcock [5] wrote "The principal challenge in therapeutics is the variability of human responses to drugs, both for good and for ill." Patient heterogeneity in both pharmacokinetics and pharmacodynamics (PK/PD) is clearly well recognised, as is the diversity of their individual values and goals of care [6]. Thus dose individualisation must become a key component in how we develop and facilitate the use of new drugs, and these individual D-E-R analyses should inform decisions regarding the optimal dosing strategy for the drug under development.

- Dosing strategies can be broadly categorised as:

    1. Individualised - based on responses (PD and/or PK) **after** giving the drug
    2. Group - based on patient covariates (PD and/or PK) **before** giving the drug
    3. Population - no dosage adaptation. Standard dosage to all patients ('one size fits all' dosing).

    In some therapeutic areas, dose individualisation using response measures may be quite straightforward (e.g. target INR with warfarin for the prevention of thromboembolisms), whilst for others the response measures may be both multidimensional (e.g. glucose control versus risk of hypoglycemia and weight gain with sulphonylureas in type 2 diabetes) and patient-specific (e.g. patients will differ in

their attitude to weight gain). In these cases, patients and their physicians deserve to have information that enables them to individualise dosing to optimize benefit/risk at the individual patient level. Where PD response measures are not available, PK measures can be used to better individualise future dosing regimens to achieve target concentrations and improve outcomes [7,8].

Dose adjustment based solely on covariates treats 'subgroup' or 'group' membership as sufficient information for individualising dose. Since patients will still be heterogeneous within each subgroup, this will often not be sufficient to yield the best outcomes for individual patients.

Dose individualisation is actively researched across multiple therapeutic areas and drugs [9, 10, 11]. Unfortunately, these efforts typically happen post-approval, with knowledge and insights not fed back into improved dosing recommendations in drug labels. This is clearly not ideal.

Key Recommendations

- Using appropriate designs and analyses, to quantify how different dose individualisation approaches perform relative to the population ('one size fits all') dosing approach.

- To encourage regulators to see the determination of optimal dosing strategies to be central to drug development, and a key element in the review, approval and informed labelling of new drugs.

- To enable the best use of certain new drugs, dose individualisation tools should be made available at approval to compliment the drug label. Looking forward, the ability of physicians and patients to both use **and** subsequently contribute (with consent) 'real world data' would enable the further refinement of dose individualisation algorithms.

Summary

- Drug development should focus on understanding. Population-average D-E-R and Individual D-E-R should be seen as parallel and complementary efforts that enable the most informed evaluation and optimal use of new drugs.

- Drug development programs should be designed to accurately and precisely estimate how both benefits and risks change as function of dose/exposure. This can be achieved only by investigating wide ranges of doses **throughout** drug development. The resulting D-E-R relationships (with uncertainty) can be incorporated into drug labelling to enable patients and their physicians to make informed decisions on dose individualisation.

- When the evidence supports scientifically based dose individualisation as superior to no dosage adaptation, dose individualisation algorithms should become a central component of the drug label.

- The above is predicated on putting science and patients first, with drug development seen as a process that learns how dose maps to both benefits and risks. As evidence accrues, sponsors and regulators can identify a range of dose sizes that merit approval. This integrated approach for both benefits and risks should be seen as the central tool for evidence synthesis, and hence requires leaving the historical bar for evidence (two studies with $p<0.05$ for benefits alone) behind.

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