Improving Clinical Study Design and Understanding via Modeling and Simulation

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Outline

- Motivation: improving efficiency of drug development
- Model-based drug development
- Benefits and challenges of MBDD
- Example: pick-the-winner design
- Concluding remarks

Motivation

- Pharmaceutical industry pipeline problem: fewer approvals, escalating development costs, high late phase attrition, tougher regulatory environment, expiring patents on blockbusters
- Traditional development paradigm not sustainable
- Innovative design and analysis methods are key priority for improving clinical development practice
  - How to make best use of available information
  - Integrate knowledge across trials, phases, programs
  - Design studies and programs to optimize information value per patient

⇨ Modeling and Simulation (M&S) has a key role to play

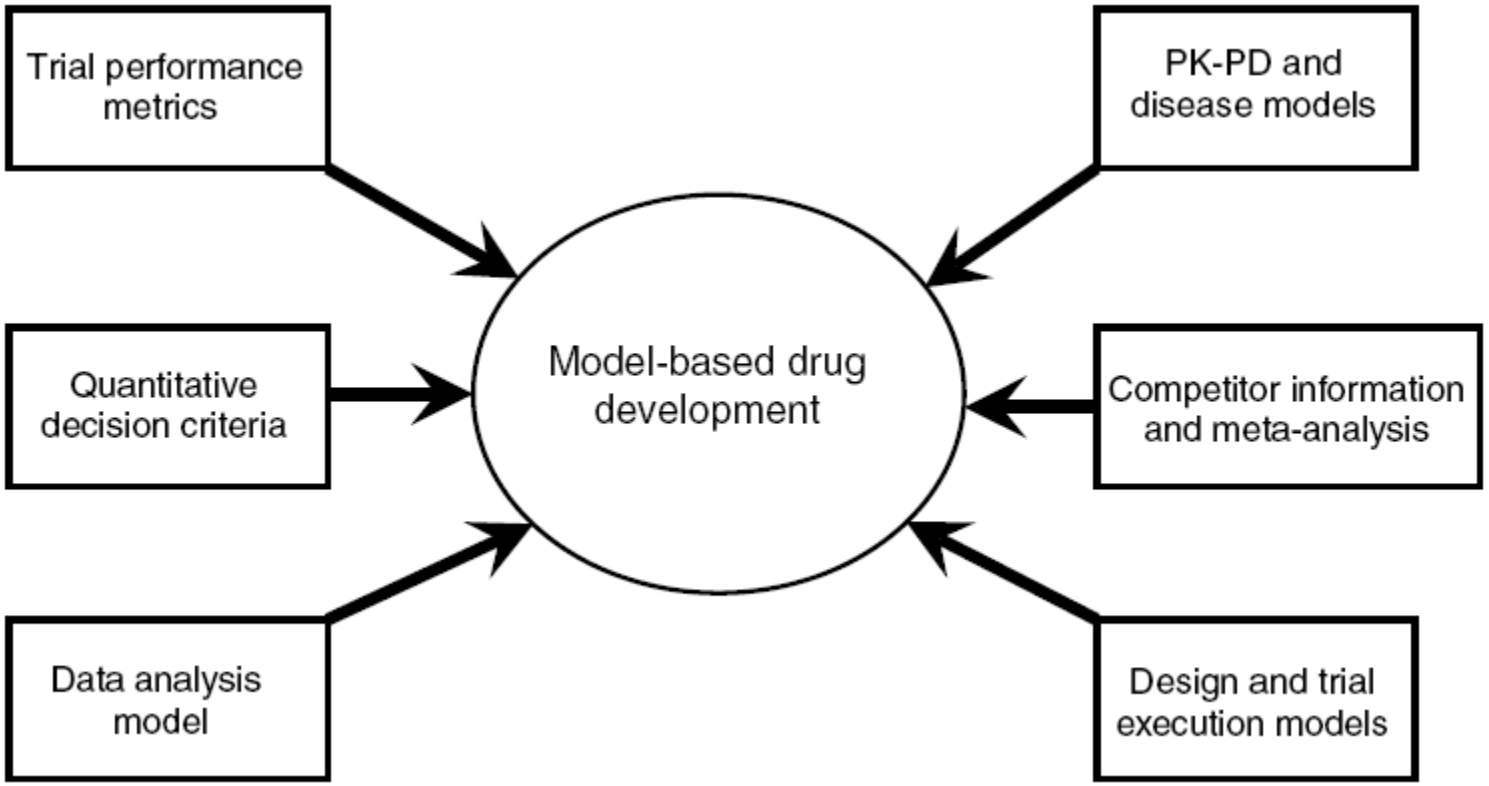
Model-Based Drug Development

- Modeling provides a framework for combining assumptions, prior information (internal and external sources), and observed data – systematic knowledge integration
- Simulations, jointly with modeling, allow exploration of alternative scenarios and evaluation of uncertainty in trials and development programs: quantification of benefit/risk for informed decision making
- Modeling and Simulation (M&S) is the cornerstone of modern development program and trial design

MBDD: overarching goal and strategy

- Move toward a drug development culture in which all decisions, from pre-clinical to marketing to portfolio management, are supported by quantitative information and integrated knowledge
- MBDD strategy for achieving this goal is to represent different elements of drug development decision process (e.g., disease progression, dose-response, recruitment rate) through models, simulate trials and development programs (under different scenarios) to evaluate possible outcomes, and integrate all information via sensible performance metrics, such as probability of success and expected net present value

MBDD components



From R. Lalonde

MBDD implementation is a multidisciplinary task

MBDD: Benefits

- Quantitative decision making: scientific thinking applied to decision process itself
  - Better informed, more accurate Go/No go decision rules
  - Flexibility to reassess assumptions during trial (adaptive design)
  - Stopping rules (futility and/or efficacy) at interim to speed up development and save resources
- Integration of information through modeling: improved knowledge efficiency across development
- Evaluation of sensitivity to assumptions used in planning via simulations: objective quantification of risk
- Increase likelihood of success, or reliable early termination
- Improved understanding of treatment effect (e.g., dose-response of efficacy and safety, subgroups effects)

MBDD: Challenges

- Resistance to change: pharma industry mindset favoring traditional development approaches – intuition-driven decisions, isolated knowledge
- Silo mentality: budgets, priorities, reward system focused on specific needs of different departments often create barriers for cross-functional knowledge integration (e.g., datasets, processes, etc)
- Lack of integrated vision of MBDD: different quantitative groups often have disparate views of MBDD – "ownership" concerns, collaboration barriers
- Cost-cutting, speed-focused environment pervasive in drug development not conducive to MBDD: moving quickly in short term does not imply later success

MBDD: Requirements

- Change management to overcome mindset hurdle
- Clear buy-in from upper-management down to teams: embrace quantitative decision making, moving away from intuition-driven approaches
- Adequate resources: increased planning, more people with proper expertise; suitable hardware and software for M&S computationally intensive methods
- Adequate operational infrastructure for information-driven approaches (e.g., adaptive designs): drug supply, recruitment, data management, etc
- Regulatory acceptance for MBDD-driven design and analysis (especially in confirmatory stage)

Example: pick-the-winner design

- Phase 2 study intended to select between two compounds to bring forward to Phase 3: an approved drug (different indication) and a new compound
- Two doses per compound (low and high) – dose selection a plus, but not required; placebo included
- Background treatment used in all arms
- Binary response, based on improvement in clinician assessment from baseline
- Expected placebo response: 25-30%; max treatment effect: 30-35%

Original design rationale

- Sample size calculation: 80% power of Cochran Mantel Haenszel (CMH) test with placebo = 30% response and active arm = 60% response (2.5% one-sided)
- Clinical team happy with design, as sample size was within budget
- Compound and dose selection to be done based on team "gestalt" after looking at unblinded data: "will know it when I see it"
- Even though neither compound had ever been used for the indication, no futility rule: "know both work"

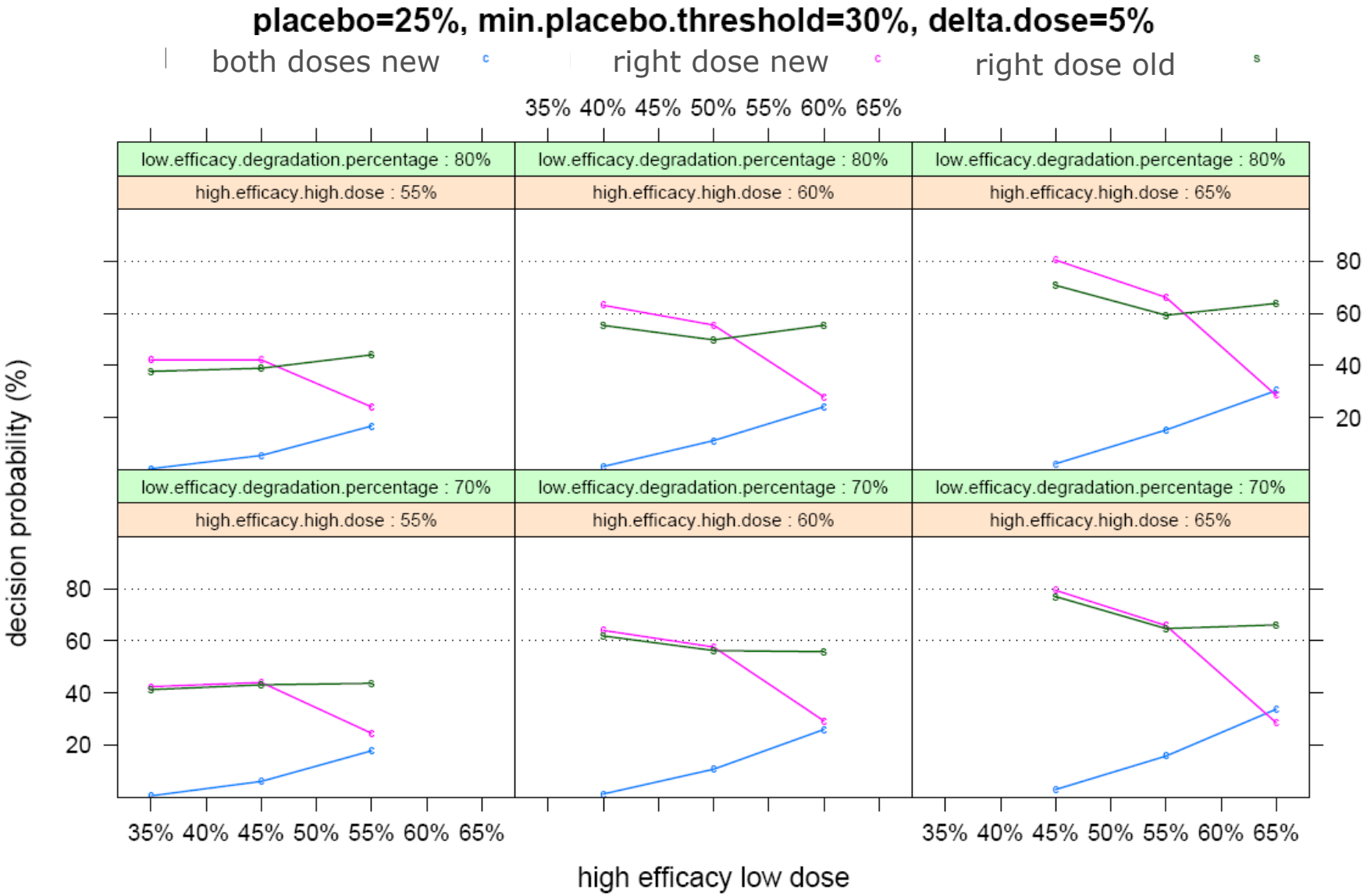
Problems with design rationale

- Based on a different question (sign. vs. placebo) than the one of greater interest (pick best compound)
- Team had no idea how well the trial would be able to pick the winner, at its end; dose selection was not initially considered, either
- No pre-specified selection rule: team wanted it entirely ad-hoc – no way to evaluate its performance
- No assessment of sensitivity to assumptions (which were based on literature and wishful thinking)
- Interim analyses not considered (operational issues, too late to make a difference, etc)

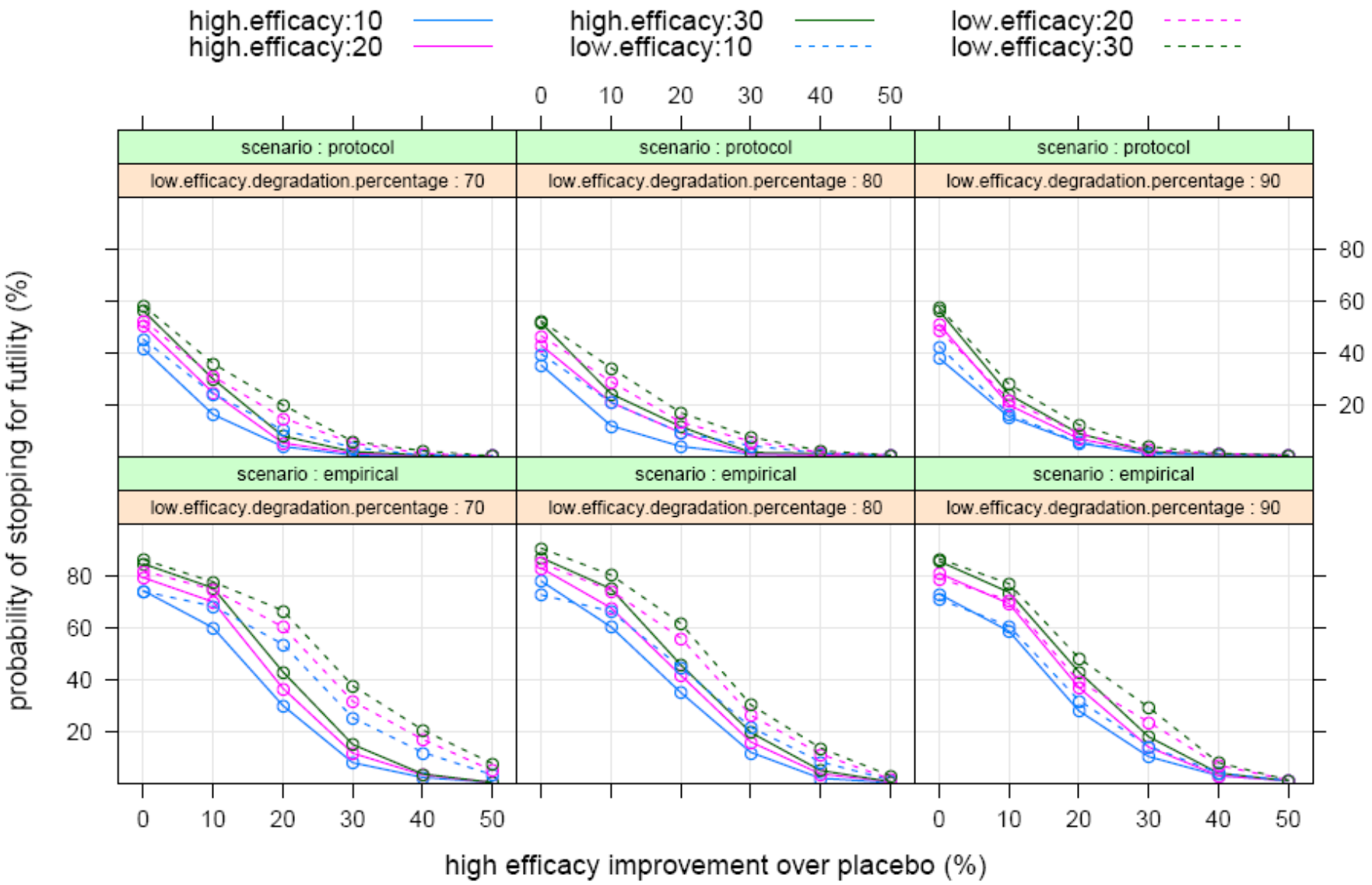
M&S evaluations

- Agreed on simplified rules for compound and dose selection, based on efficacy response only: only 1 dose of approved compound, but 1 or 2 of new compound
- Included futility rule for dropping dose/compound
- Variety of scenarios to explore sensitivity of selection and futility rules
- Derived operating characteristics of decision rules and hypothesis tests under different scenarios, e.g.:
  - Probability of selecting "right" compound and dose
  - Probability of stopping dose or compound for futility

Pick-the-winner probabilities



Futility stopping probabilities



Concluding remarks

- MBDD can become a paradigm shift in drug development, but needs a corresponding "thinking shift" among decision makers in industry and regulatory agencies to become successful
- Within companies, activity may need to reside in separate group to minimize ownership issues (e.g., does it belong to Biostat, Clin Pharm, etc?)
- New professional group associated with MBDD: pharmacometricians; training programs still lagging behind (academic degree, etc)
- Increasing use of M&S is inevitable, but road ahead may be a bit bumpy