



FDA PUBLIC MEETING

PROMOTING EFFECTIVE DRUG DEVELOPMENT PROGRAMS: OPPORTUNITIES AND PRIORITIES FOR FDA'S OFFICE OF NEW DRUGS

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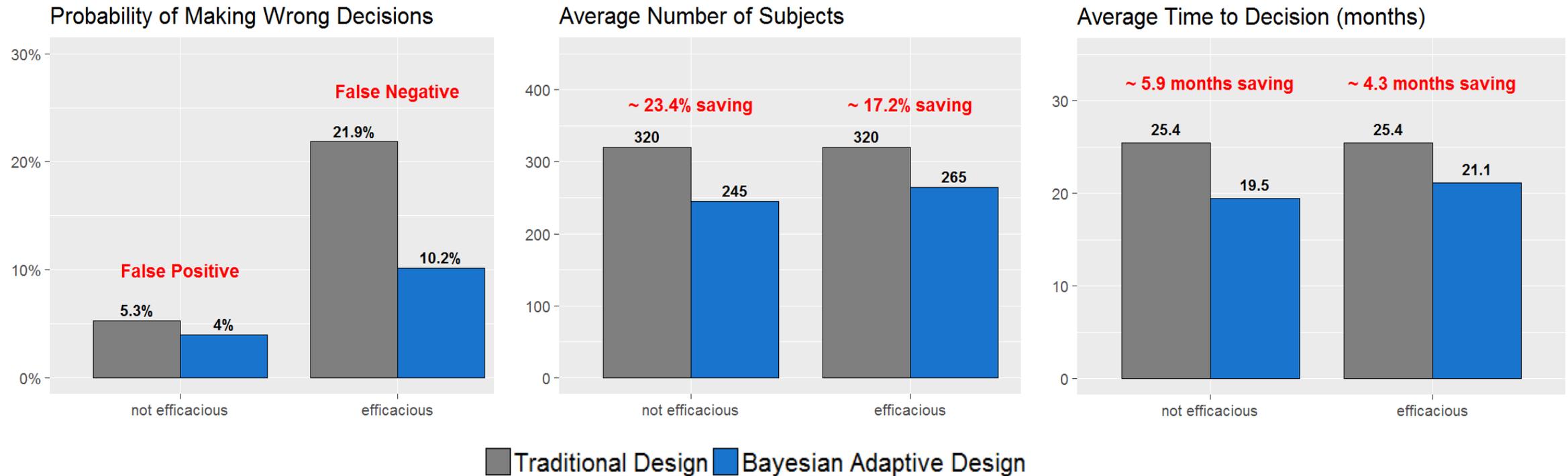
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TOPICS FOR DISCUSSION

1. Facilitating greater use of innovative trial designs
2. Determining sufficiency of FDA's Sentinel system to evaluate drug safety issues

TRIALS LEVERAGING ADAPTIVE DESIGNS CAN MORE EFFICIENTLY FAIL AND SUCCEED, REDUCING SAMPLE SIZE AND TIMELINES WHERE APPROPRIATE



*Based on 10000 simulated trials (data on file)

*Bayesian adaptive design includes features of Bayesian interim success/futility, adaptive randomization and longitudinal modeling

INNOVATIVE TRIAL DESIGNS: 3 AREAS OF OPPORTUNITY

1. Provide Timely FDA Advice and Engagement
2. Ensure Sufficient Statistical Capacity
3. Facilitate Global Approaches to Innovative Trials

PROVIDE TIMELY FDA ADVICE AND ENGAGEMENT: *CHALLENGES AND RECOMMENDATIONS*

CHALLENGES

- The Complex Innovative Trial Designs (CID) pilot provides a good opportunity to address issues related to novel designs. However, more timely and iterative FDA advice is needed. Approaches taken for various aspects of innovative trials may be untried and require rapid feedback from FDA to reduce sponsor risk. These approaches involve statistical aspects (modeling and simulation, methods to address bias or missing data) and operational aspects (data collection methods, safety reporting).

RECOMMENDATIONS

- Office of New Drug (OND) Policy should publish learnings from implementation of guidance as they accumulate. Options could include use of FDA's website or a Q&A document. Case studies that illustrate or expand upon previous guidance would be helpful, as well as advice on design features that FDA has found unacceptable.
- OND Policy should identify best approaches for sponsors to obtain quick, targeted feedback to minimize regulatory uncertainty.

ENSURE SUFFICIENT STATISTICAL CAPACITY: *CHALLENGES*

- Advancing use and acceptance of innovative trial designs is only possible when the agency is staffed with the right expertise.
 - The statistical discipline must be adequately staffed to review protocols for innovative trials, and the agency's clinicians must be familiar with the underlying tools and techniques.
- The review team's statistical and clinical experts should be aligned in their advice.
 - Coordination is key to ensure that sponsors receive advice based on current best practices regarding Bayesian designs, modeling and simulation to evaluate trial operating characteristics, and other novel approaches.

ENSURE SUFFICIENT STATISTICAL CAPACITY: *RECOMMENDATIONS*

- FDA should enhance its statistical capacity on Bayesian adaptive designs and modeling and simulation so that it can provide timely review and advice on the rapidly increasing use of innovative trial designs.
 - In the context of FDA's well-known hiring challenges, the agency could consider contracting with third party experts for support while FDA recruits additional expertise.
 - Similarly, industry should address internal capacity issues. Amgen built a centralized, robust modeling and simulation group to improve decision making in drug development to enable evidence-based, simulation-guided, innovative designs.
- FDA should ensure that statistical and clinical disciplines are collaborating closely and providing the necessary advice to advance drug development programs.
 - In February 2019, Amgen participated in an innovative design modeling and simulation training session for FDA biostatisticians. OND Policy could consider a similar exercise for clinical review staff to promote broad familiarity with relevant tools and techniques.

FACILITATE GLOBAL APPROACHES TO INNOVATIVE TRIALS: *CHALLENGES*

- The global nature of drug development programs means that lack of regulator alignment will affect a sponsor's willingness and ability to pursue innovative trial designs in support of global registration.
 - Advice provided by regulators on innovative designs can sometimes be different or conflicting, increasing the uncertainty of pursuing an innovative approach.
- Progress in advancing innovative trial designs will be difficult without more frequent and substantive regulator-to-regulator discussions on this issue.

FACILITATE GLOBAL APPROACHES TO INNOVATIVE TRIALS: *RECOMMENDATIONS*

- OND should consider a “cluster” approach with its agency peers where they discuss sponsor proposals for innovative trial designs intended for use in global development programs.
- OND should also engage other regulators and stakeholders in public discussions about guidance for novel trial designs.

POST-MARKET SAFETY STUDIES: RELEVANT CURRENT LAW

- In 2007, Congress authorized FDA to require post-marketing safety studies to assess a known serious risk, to assess signals of serious risk, or to identify an unexpected serious risk when available data indicate there is potential.¹
- Congress also directed FDA to establish an active post-market risk identification analysis system → **Sentinel's Active Risk Identification and Analysis (ARIA) System.**²
- However, before requiring a post-market safety study, FDA must first determine that adverse event reporting and ARIA will not be sufficient to assess or identify the risk.
- By mid-2017, after significant investment from FDA's budget authority and user fee revenue, Sentinel included 425 million person-years of observation time.³

1. Section 505(o)(3) of the Food, Drug, and Cosmetic Act (FDCA)

2. Section 505(k)(3) of FDCA

3. FDA Sentinel System Five-Year Strategy 2019-2023

<https://www.fda.gov/media/120333/download>

PREGNANCY REGISTRIES PROVIDE AN EXAMPLE OF SENTINEL SUFFICIENCY ISSUES: *CHALLENGES*

- FDA's October 2019 guidance¹ on Sentinel is helpful, however it is unclear how FDA applies the outlined approach in specific drug development programs.
 - FDA informs sponsors in the approval letter when it has determined Sentinel is not sufficient, but does not provide a reason or analysis. There is little transparency regarding FDA's process.
- Pregnancy registries are a good example of the issue.
 - FDA's primary approach to assessing drug safety in pregnant women is through prospective exposure registries (i.e., pregnancy registries), even if the intended patient population does not include women of childbearing age.
 - FDA's May 2019 draft guidance² acknowledges the limitations of pregnancy registries (e.g., low enrollment, high loss to follow-up, lack of exposure, low statistical power to detect associations). However, FDA has not been receptive to alternative proposals, such as claims-based active surveillance programs.
 - Pregnancy registries have many implementation challenges and take a long time to complete, limiting their public health impact. We need alternative ways to evaluate the safety of therapies during pregnancy.

1. Draft Guidance, *Postmarketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*, October 2019.

2. Draft Guidance, *Postapproval Pregnancy Safety Studies*, May 2019.

PREGNANCY REGISTRIES PROVIDE AN EXAMPLE OF SENTINEL SUFFICIENCY ISSUES: *RECOMMENDATIONS*

- Consistent with the October 2019 guidance on Sentinel, FDA should be transparent in communications with the sponsor regarding whether Sentinel is sufficient to evaluate a known or suspected serious risk.
 - When FDA imposes a post-market safety study, FDA should provide an analysis and rationale for why Sentinel is not sufficient.
- FDA should conduct a robust evaluation of whether Sentinel is sufficient to generate appropriate post-approval evidence of drug safety during pregnancy for a particular drug, prior to addressing alternative approaches.
 - Sentinel has been in place for 12 years, and FDA is required by law to evaluate the system before imposing a pregnancy registry, or other pregnancy safety study.
- If FDA determines that Sentinel is not sufficient, FDA should consider whether another type of database study is sufficient, before requiring a pregnancy registry.
 - FDA acknowledged this approach in the October 2019 guidance. Companies have internal observational research capabilities that could be useful.