R&D SENIOR LEADERSHIP BRIEF

The Adoption and Impact of Adaptive Trial Designs

Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

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Tufts CSDD hosted and facilitated a Senior Leadership roundtable on February 13, 2013 in Boston to discuss the adoption and impact of adaptive design clinical trials. Forty senior executives from a variety of cross-functional areas participated including clinical research and development, biostatistics, project management, and clinical operations. In addition, perspectives from the Food and Drug Administration (FDA) and European Medicines Agency (EMA) were represented.

For the purposes of this roundtable, participants defined adaptive clinical trials as:

> **Preplanned adaptations — generated through the use of trial simulations and scenario planning — of one or more specified clinical trial design elements that are modified and adjusted while the trial is underway based on an analysis of interim data**

This definition is consistent with that provided in the current regulatory guidance.

In addition to facilitated discussion, Tufts CSDD presented the results of interviews conducted among directors and heads of statistical functions from a dozen major pharmaceutical companies and provided forecasted impact metrics based on a simple model of trial design adaptation. A large pharmaceutical company also presented a case study on implementing adaptive trial design practices at the portfolio level throughout the organization.

This Senior Leadership Brief summarizes key takeaways from the roundtable.

Overall Adoption

1. Across the industry, simple adaptive designs are used on approximately 20% of clinical trials. Participating companies report that they expect the adoption of adaptive trial designs in exploratory phase clinical trials to increase significantly over the next several years.

2. Simple adaptive trial designs – such as early study terminations due to futility – are becoming widely adopted throughout the industry, most notably in phase III studies.

    - Roundtable participants unanimously agree that study terminations due to futility are relatively easy to implement.

    - Most organizations agree that futility analysis should become a standard practice in phase II and phase III studies, across all therapy areas.

    - Sample size re-estimation is viewed by some large pharmaceutical companies as a simple adaptive design. Reported adoption of this approach appears to be low relative to use of futility stopping.

    - Although a number of case examples of sophisticated adaptive designs exist, the adoption of these designs – including adaptive dose-finding and seamless phase II/III studies – has been slow.

    - Roundtable participants note that more sophisticated adaptive designs applied to exploratory phase clinical trials hold strong potential to impact success rates in later phase development.

    Most participants express limited interest in seamless phase II/III studies as this approach may generate results that are difficult to interpret.

3. Internal organizational resistance is one of the primary factors limiting enterprise-wide adoption of adaptive trial design approaches. Support and guidance from regulatory agencies does not appear to be a major barrier to adoption.

4. Operating concerns -specifically delays and disruptions in trial execution, patient participation and distribution of clinical supplies – are the largest perceived barriers.

5. Other major barriers to adoption include questions and concerns about how to monitor data without introducing bias; the lack of adaptive trial design experience among both internal development teams and external contract research organizations; gaps in infrastructure and technology to implement more sophisticated adaptive designs; and the limited capacity of independent data monitoring committees.

6. Participants perceive that regulatory affairs functions are risk averse to adopting sophisticated adaptive design approaches due to their belief that more clarity from regulatory agencies is needed.

7. Regulatory agencies, in contrast, appear highly receptive to exploratory phase adaptive trial designs (e.g., adaptive dose-finding studies) to challenge and inform clinical teams prior to committing to pivotal late-phase studies. Regulatory agencies are concerned that early development approaches are not efficiently detecting failures prior to phase III or that decisions taken in exploratory development are sub-optimal and lead to unnecessary phase III failure. The use of adaptive design in exploratory development may help address both concerns.

Areas of Impact

- Roundtable participants note that adaptive trial designs are already offering cross-functional teams within organizations, new insights into study design through scenario planning and trial simulation prior to finalizing the protocol. 'Stress-testing' the protocol is becoming a critical stage of development planning.

- Tufts CSDD estimates that early study terminations due to futility and sample size re-estimation applied across the portfolio -- could save sponsor organizations between $100 million and $200 million annually in aggregate costs (direct and indirect costs) depending on portfolio size and development cycle time savings.

- Adaptive trial designs may save substantial financial resources by helping to reduce the number of protocol amendments. According to Tufts CSDD research, the implementation of each amendment costs organizations nearly half-a-million dollars ($US) in direct costs and requires 60 days to implement.[1]

- Roundtable participants anticipate that using adaptive trial designs to perform phase II dose response assessments will dramatically improve phase III dose selection, delivering substantially higher value through improving late stage success rates. Importantly, this is the area where regulatory agencies see the most benefit from adaptive design.

Recommendations for Implementing Enterprise-Wide Adoption of Adaptive Design Practices

A global top 20 drug development company that has been applying simple adaptive trial designs to phase II and III studies across its portfolio for five years led this portion of the roundtable discussion. The company reports saving more than $70 million each year through adoption of simple

[1] Getz K, Zuckerman R, Cropp A, Hindle A, Krauss R, Kaitin K. Measuring the incidence, causes, and repercussions of protocol amendments. Drug Information Journal 2011;45:265-75.

adaptive dose-finding studies in phase II and sample size adjustments and futility stopping in phase III. Key takeaways from the discussion:

- Senior management education, buy-in and strong support are critical first steps in driving adoption of adaptive design trials.
- In a number of organizations, cross-functional support made up of experienced drug development professionals with expertise in clinical pharmacology, clinical, operations and statistics have played an important role in supporting adoption.
- Measured and publicized cost savings from the use of adaptive designs (e.g., futility analysis) is an essential ingredient in convincing organizations – particularly senior management – to continue to support and extend adoption.
- Statisticians have been instrumental in helping shape the current regulatory guidance and in promoting the benefits of adaptive designs. However this group alone does not appear capable of driving industry-wide adoption. Organizations that have established strong proponents among therapy area heads, medical experts and clinical operations professionals in addition to statisticians are far more effective in driving successful adoption.
- For most organizations, the adoption of adaptive designs is most effectively started with simple and straightforward adaptations (e.g., sample size re-estimation and futility analyses). Simple designs applied across the portfolio are deemed far more beneficial and practical than more complicated designs applied to a few select studies. Doing so eases the organization into implementing adaptive designs across the portfolio and facilitates a smoother transition to more sophisticated approaches.
- Other organizations have found that implementation is most successfully facilitated through internal adaptive trial design experts working with individual clinical teams to apply the 'best' design regardless of its simplicity or sophistication. Trial simulation and scenario-planning are key to identifying the 'best' design and to ensuring its broad acceptance.
- The adoption of more sophisticated adaptive designs in exploratory development may necessitate the use of new technologies and working practices and will require organizations to re-evaluate their existing clinical operating processes.

There is a significant amount of industry attention, investment and activity on improving clinical trial quality and efficiency (e.g., risk-based monitoring approaches). Coupling adaptive designs with these industry initiatives holds strong promise to address the challenge of improving R&D performance, quality and cost.

About Tufts CSDD Sponsored Research Projects

Our Sponsored Research projects typically focus on operational or R&D management issues, and may entail creation of a multi-company working group, survey creation, leadership/management roundtables, collection of company data, and publication of aggregate analyses. Individual participating companies may also receive customized reports like this one, summarizing the data collected, or comparing their benchmarks against an industry mean when applicable.

As part of Tufts CSDD Sponsored Research programs, customized Senior Leadership Roundtables provide a unique opportunity for senior pharmaceutical and biopharmaceutical leaders to engage in frank and open discussion on a wide variety of R&D strategies and practices, and share ideas with industry peers and regulators in a neutral setting. Visit our website at http://csdd.tufts.edu/sponsored_research to learn how to partner with Tufts CSDD on a research initiative.

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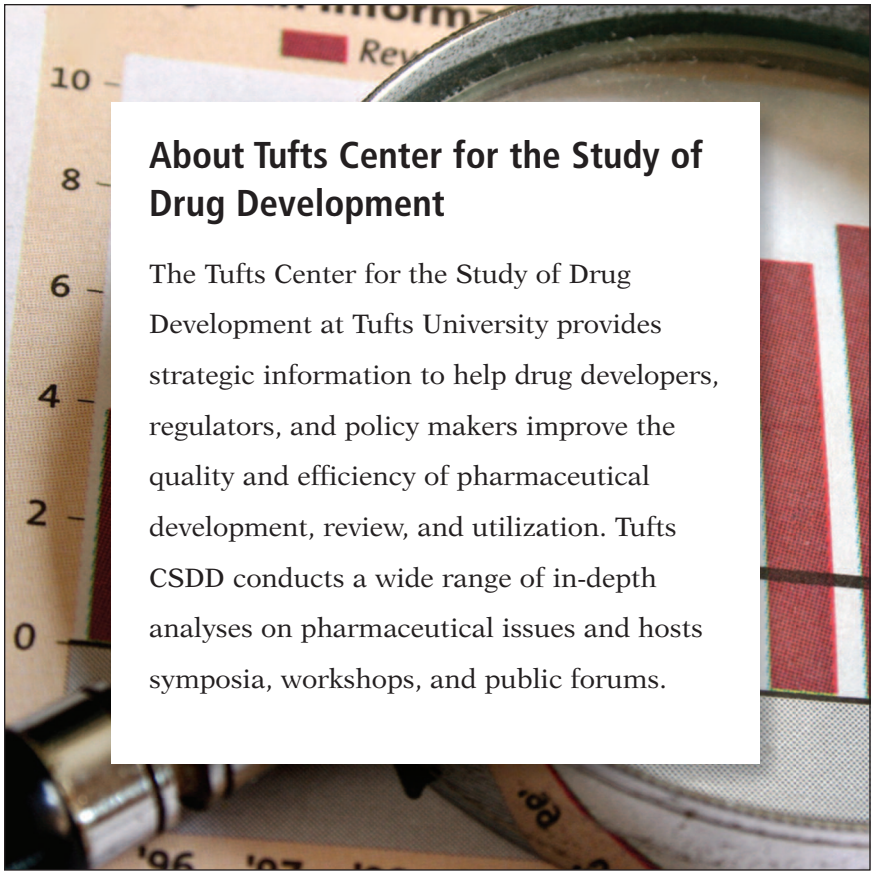

About Tufts Center for the Study of Drug Development

The Tufts Center for the Study of Drug Development at Tufts University provides strategic information to help drug developers, regulators, and policy makers improve the quality and efficiency of pharmaceutical development, review, and utilization. Tufts CSDD conducts a wide range of in-depth analyses on pharmaceutical issues and hosts symposia, workshops, and public forums.

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