Take The Pain Out Of Clinical Trials; Use Statisticians Early

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Executive Summary

As a research pharma or biotech, you face a complex and regulatory-heavy environment. New developing products make competition fierce, while a trend in regulatory control of protocols and funding has created myriad challenges for building a case to maintain funding levels year over year.

To keep time and funds spent during the clinical phases reduced and the information provided by subjects maximized, you may want to take a new look at the teams and professionals you use, and how you use them. Statisticians for one, can play a key role in efforts to enhance, optimize, and reengineer process and operations.

The Troubled Impact of Late Statistician Involvement

Many bad things happen that cost you time, money, aggravate investors, waste patient time and hinder advances. For instance, protocol amendments are costly in both expenditures, and time - they may even reduce the usefulness of data already collected, and when amendments *could* have been avoided with innovative and attentive planning, well, investors become aggravated. When statisticians are contacted only after the protocol is finalized, or worse, after the first patient has been recruited, then the opportunity for an innovative design is lost. On the other hand, partnering with a qualified statistician early during the clinical phases of development of your drug or medical device has the impact of expediting the development lifecycle.

Expanding Thought To Leverage Know-How

Changes in the drug and device development landscape have made it critical to diversify protocol development and expand thinking to include how qualified statisticians can deepen the value and scope of your strategy beyond what has been "good enough" in the past. Today's most successful trials leverage the skills of the people you once used only *after* the trial was designed to be part of the trial planning process and accomplish the following:

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- Develop a statistical strategy that transcends multiple clinical trials and phases, aligns with regulatory requirements, and adheres to business constraints
- Provide quantitative evidence to support choice of strategy by simulating alternative strategies
- Reduce downtime between clinical phases using planned seamless transitions
- Leverage early-phase learnings in late-phase development to reduce sample sizes
- Turn developing information into deliverables to expedite submissions or investors' due diligence

This is particularly important for small and mid-sized pharmaceutical and biotechnology companies which often lack in-house statisticians and data managers to participate in planning trials.

Let's use two case studies to examine the value realized by biopharmaceutical and medical device product developers when statisticians are included in product development planning.

Case Study I

A biotech is developing a treatment for sexual dysfunction. A phase 2 study provided many learnings, including that there is a substantial placebo effect, that patient-to-patient variability is very high, possibly masking an efficacy signal, and that patient characteristics such as age and concomitant medication use contribute to safety and efficacy response variability. Feedback from a regulatory authority identified three challenges:

1. The optimal dose had not been adequately characterized
2. The recommended time between self-dosing and sexual activity had not been defined
3. A contra-indicated population must be studied for safety due to concerns about off-label use.

The biotech strongly believes that the concerns are unfounded and therefore wants to move to a confirmatory study with utmost speed due to competitive pressures. So how does one address the regulatory concerns at as little expense of time and money as possible?

An Answer to the Challenge

Develop a one-study design that addresses regulatory concerns, leverages the phase 2 information and minimizes time between phase 2 and 3. Meaning, an interim analysis is pre-specified to:

a) Select the dose to carry forward to the two-arm phase 3 study

b) Select the lapsed time between dosing and sexual activity to recommend to subjects during phase III and labeling.

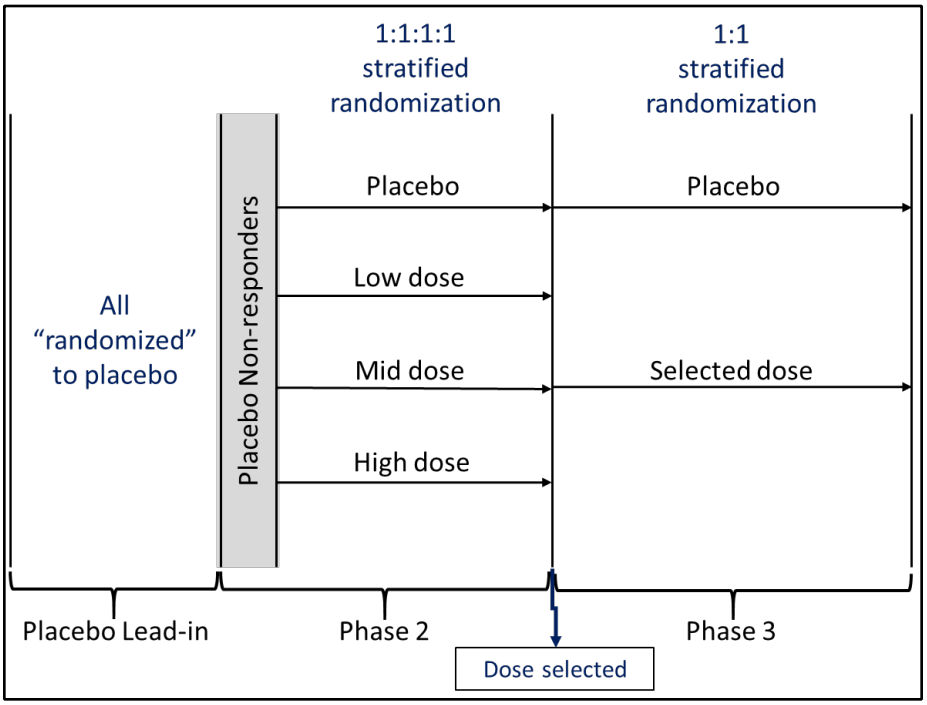
c) Confirm the sample size needed to maintain desired power for phase III.

Each regulatory concern is addressed using seamless phases, interim analyses, and stratification. Notice how each design feature addresses a sited issue:

a. Issue: The optimal dose has not been adequately characterized. **Design Feature**: Include a phase 2 with multiple doses.

b. Issue: Time between self-dosing and sexual activity. **Design Feature**: During the interim analysis, analyze the relationship between time between dosing and activity and efficacy response. Recommend to subjects in phase 3 the length of time realizing the best response in phase 2.

c. Issue: Contra-indicated population safety. **Design Feature**: Include a stratum comprised of subjects with the contra-indication. This arm is studied for safety only, and is not included in the primary phase 3 analysis.



In addition to the regulatory concerns being met, the challenges indicated by the phase 2 study are addressed via the placebo lead-in, stratification, and an interim analysis.

1. The placebo effect is greatly reduced by screening out subjects who respond to placebo during the placebo lead-in phase.
2. The high variability between patients is reduced by stratifying randomization according to factors known to contribute to the variability, such as age and concomitant medication use.
3. The biotech's desire to move swiftly into phase 3 is addressed by the seamless nature of the design. Whereas stand-alone phased trials result in many months down-time between phases, the seamless design requires only

enough time to leverage the interim analyses to refine the design of the next phase; best performing dose, optimal dose-to-activity time lapse, and sample size confirmation.

Keys to success

There were several key factors leading to the design development. The statisticians developing this design:

- Were provided all minutes from key meetings and relevant correspondence between the biotech and the regulatory authority.
- Had access to the biotech's key opinion leaders who provided subject matter expertise regarding contributing factors to variability, causes for the placebo effect, and design reviews.
- Had access to the regulatory strategist who rated the probability of regulatory acceptance of alternative design features.
- Were granted approval by the biotech to expend the effort to simulate the entire phase II/III design using the data from the earlier phase II study to run different scenarios (assumptions). The scenarios differed by assumed (stratified) response levels, variability, recruitment rates, and other factors of interest to the biotech. The results included statements regarding the probabilities that each dose would be selected, the time required to run the entire study, and probability if detecting a significant difference from placebo. These results supported such decisions as whether to proceed and the number of sites to use.

Enriching The Composition & Meaning Of Data

These benefits can only be realized by partnering with a qualified team of statisticians. "Team" is important; statisticians need colleagues to share ideas and criticisms. The statistician's toolbox is chock full of possibilities that can be applied in various combinations and sequences: including,

1. Operationally seamless designs for phases I and II, or II and III – where objectives are combined into one trial
2. Inferentially seamless designs for phases I and II, or II and III – where data can be combined across trials
3. Adaptive Designs - including: dose selection, sample size re-estimation, play-the-winner, drop-the-loser, and adaptive randomization
4. Interim Analyses – for futility or efficacy
5. Statistical Models - To simulate the results of one or more phases of development using different assumptions
6. Bayesian Inferential Methods - To leverage prior knowledge
7. Design Features - For instance: cross-over, enrichment, stratification, non-inferiority, repeat measures, multiple endpoints, and others
8. Variety in Analysis Models - Such as: subject-level models, competing risks, propensity scores, and ordinal models

A trusting partnership is particularly crucial for small and medium sized pharmaceutical and biotechnology companies, which often lack in-house statisticians and data managers to help plan and run trials and deal with regulatory agencies and top management, we can see that partnership in play in the successful case study below.

Case Study II

A biotech is developing a treatment for cancer. The target population is small because it includes only those patients for whom the standard of care has failed; about 25% of all treated. The target cancer has two tumor types; one can be resected before treatment, the other cannot. Failure of the standard of care occurs in two ways; refractory (quickly) and relapsing (after initial response). Feedback from multiple regulatory authorities include the following three issues:

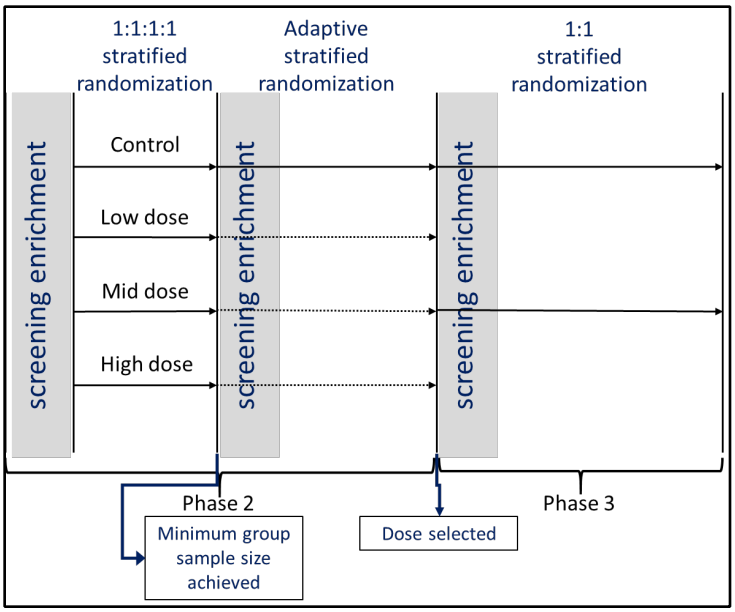
1. The dose has not been adequately researched due to a change in product formulation; the sponsor must justify the selected dose with respect to both safety and efficacy.
2. The sub-populations defined by the two tumor types must be studied separately because one set of patients is disease free (resected) at baseline and the other is not (cannot be resected).
3. To separate the treatment effect from the benefit of tumor resection for one of the sub-populations, a control arm is recommended.

So how does one design a study that addresses regulatory concerns while expediting product development to ensure research funding?

An Answer to the Challenge

A seamless phase II/III design with an enriched and stratified sample population in which patients are adaptively randomized to the most promising dose. This addresses regulatory concerns, accounts for the complexity of the target population, and acknowledges business constraints.

1. Issue: One set of patients is disease free at baseline and the other is not. **Design Feature**: Enrich the sample using a biomarker that screens patients for probable standard of care failure rather than waiting for failure to occur. This allows randomization while all patients, regardless of tumor type, are disease free.
2. Issue: The dose has not been adequately researched. **Design Feature**: incorporate a dose selection phase where patients are more likely to be randomized to active doses that demonstrate efficacy and a good safety profile.
3. Issue: Separate the treatment effect from the benefit of tumor resection. **Design Feature**: Include a control arm in which treatment is standard of care.
4. Issue: Need to minimize the number of patients and the time to end of Phase 3. **Design Feature**: Seamless Phase 2/3 where patients from Phase 2 on the correct dose can be carried forward for the final analysis.



This design addresses the biotech's constraints by minimizing the number of patients treated with a sub-optimal dose by adaptively randomizing patients. Treatment efficacy and safety is measured on an earlier time point compared to the primary endpoint for the phase 3 analysis. This allows patients randomized to the "winning" dose during phase 2 to be included in the final phase 3 analysis.

Keys to success

There were several key factors leading to the design development. The statisticians developing the design:

- Were provided all minutes from meetings and correspondence between the biotech and regulatory authorities.
- Had open and honest communication with the biotech regarding business constraints and expectations.
- Had access to the biotech's key opinion leaders who were responsible for raising the possibility of using the biomarker for enrichment.
- Had access to the regulatory strategist who rated the probability of regulatory acceptance of alternative design features.

Conclusion

The two case studies presented in this white paper highlight the value realized by biopharmaceutical and medical device product developers when statisticians are included in product development planning. The time spent during the clinical phases can be greatly reduced and the information provided by each subject maximized when a statistician is involved. The keys to success in these two case studies include:

- The statisticians were involved early, while the protocol was still under development. If statisticians are contacted only after the protocol is finalized, or worse, after the first patient has been recruited, then the opportunity for an innovative design is lost.
- The statisticians were included in discussions with regulatory strategists, business decision-makers, and key opinion leaders. The information each role provides contributes to the design options and decisions.
- Relevant concerns by regulatory authorities and stakeholders were provided to the statisticians. This information guides the statisticians to only present options that are acceptable to stakeholders and address key concerns.
- The statisticians were allotted time to gather requirements, assess available information, analyze existing study data, and simulate possible outcomes. These weeks spent during planning shaved months off of study timelines and countless tens of thousands of dollars off of expended budgets.

Reference

Thall, PF Nguyen, HQ. Adaptive randomization to improve utility-based dose-finding with bivariate ordinal outcomes. *Journal of Biopharmaceutical Statistics*, 22: 785–801, 2012

About The Author

John Amrhein is Vice President of McDougall Scientific where he manages service delivery, oversees McDougall's computing infrastructure, and supervises McDougall's sales and marketing activities. John is most known for leading edge statistical designs and analyses, leveraging analytical methods to manage risks, market products, and provide real-world evidence to support decisions. John is Chair of SAS Global Forum 2017, the annual conference of SAS® Users World-Wide.

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