**CID Case Study: Master Protocol to Study Chronic Pain**

**Study Design**:

This proposal is for a master protocol designed to study chronic pain.

Master protocol designs are used in situations where one overarching protocol is designed to answer multiple questions (FDA Guidance for Industry: *Interacting with the FDA on Complex Innovative Clinical Trial Designs for Drugs and Biological Products*), such as whether multiple interventions are effective in multiple diseases. This proposed master protocol permits multiple sub-studies to investigate proof of concept for several investigational products that may be intended to treat several types of chronic pain.

Each sub-study will have a standard randomized, double-blind, placebo-controlled multi-week period with the primary endpoint being change in pain from the beginning to the end of this period. The analysis for each sub-study, however, will borrow information from the previously conducted and ongoing sub-studies that are considered relevant (either the same type of chronic pain being studied, or the same treatment being used to treat a different type of chronic pain).

**Innovative Characteristics**:

FDA considers the following trial design features to be innovative, making it appropriate to review the design under the Complex Innovative Trial Design (CID) pilot meeting program:

- Borrowing of placebo information from sub-studies of different investigational products for the same type of chronic pain.
- Borrowing of treatment effect information from sub-studies for the same treatment for different types of chronic pain.

**Potential Benefits of Design:**

- The borrowed information can reduce the number of patients that would be needed in subsequent sub-studies. The master protocol allows study design and conduct to be standardized across the various sub-studies, ensuring that the information collected in the master protocol remains relevant to the greatest extent possible across the various sub-studies.

**Considerations for the Proposed Design:**

- What is the impact of the borrowed information?
- How do the different approaches of weighting borrowed information vary?
- What happens if the placebo response changes over time?
- Are there approaches to borrow more strongly from data that is believed to be more relevant, such as by placing greater weight on more recent studies than older studies or on diseases that are considered to be more similar to the current disease?

**Simulations:**

The sponsor conducted simulations to evaluate the impact of the borrowing on the clinical trial operating characteristics. The primary purpose of this master protocol is informing the decision regarding which products are worthwhile to continue developing and obtaining accurate estimates of how effective the current drug is. Consequently, the sponsor's simulations focused on assessing the accuracy and precision of the estimates with the borrowed data which was measured using the bias (defined as the difference between the true and the model estimated value with the borrowed data), the treatment difference standard error (which is a measure of the variability of the estimate), and mean-squared error (defined as the sum of the square of bias and the square of the standard error of the estimate).

If the borrowed information from other sub-studies and the information in the current sub-study are aligned, then borrowing increases precision compared to not borrowing. When there is a difference between the borrowed information and current information, borrowing introduces a bias in the estimates which starts to decrease the overall accuracy and precision (e.g., as measured through the mean-squared error). This effect is known as a bias-variance trade-off. If the difference between the borrowed and current information is large enough, then the operating characteristics of the analysis are worse than if the previous data were ignored. Each method will produce a range of outcomes where the bias-variance trade-off makes borrowing beneficial and this window of benefit depends on the specific method used.

The sponsor conducted simulations for two different informative prior distribution types: Bayesian hierarchical modelling and commensurate priors. Both methods include tuning parameters that control the weight placed on the borrowed data and rely on assumptions about the relationships between the borrowed and current data. When less weight is placed on the borrowed data, the peak efficiency gains are smaller, but the window of benefit (with respect to bias-variance tradeoffs) widens. The objective of the simulations for future sub-studies of specific investigational products will be to identify the method and tuning parameter values that maximize the peak benefit, while preserving a desirable window of benefit.

Overall, the trade-offs resulting from borrowing data appear to be reasonable in the proof-of-concept master protocol context, though evaluation of the historical evidence to support the assumptions of the borrowing approach is critical, in conjunction with planned sensitivity analyses to evaluate sensitivity to the borrowing approach and the modelling assumptions.

**Discussion:**

While the proposed CID master protocol design is considered proof-of-concept, FDA accepted the CID into the pilot program due to the valuable learning opportunity – a pillar of the CID program – especially given concerns about the impact of borrowed data on the accuracy and precision of treatment effect estimates.

The primary assumption necessary to use the Bayesian borrowing methods proposed in this design (hierarchical modelling and commensurate priors) is known as exchangeability. This assumption means that we believe that the probability associated with the outcome is independent of the label assigned.

For example, if we know one group receives a different background/rescue therapy known to be more or less effective than the background/rescue therapy the other groups receive, then this assumption is not accurate. A similar logic applies if one group is composed of less severe patients than the other. Some issues that might impact exchangeability can be mitigated by aligning the conduct of sub-studies of different investigational products and pain types using the master protocol structure, for example, use of a common placebo and alignment in the patient assessments and associated timing. However, not all issues can be mitigated this way and so methods that do not rely on the exchangeability assumption may need to be considered.

In general, the available historical data should be used to evaluate suitability of the prospective methods and their associated assumptions. For example, a long history of a consistent placebo response supports the use of exchangeable methods for borrowing the placebo response. Likewise, the relationship between effects of other treatments across different pain types can be used to evaluate the suitability of the modelling assumptions. For example, if a treatment with a similar mechanism is shown to be effective in a particular pain type but not in a second pain type, the exchangeability assumption may not be plausible between these pain types. Planned sensitivity analyses exploring robustness to assumption violations are also ideal.

In summary, the master protocol and the employed borrowing methods can increase the efficiency of trials. The borrowing methods rely on modelling assumptions regarding the applicability of the borrowed data, and the suitability of these modelling assumptions should be supported by careful evaluation of the historical data, where available, along with simulations to evaluate design and analysis operating characteristics. Where these assumptions do not hold, alternative methods that do not rely on these assumptions can also be considered.

**Reference:**

Guidance for Industry: *Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products* https://www.fda.gov/media/130897/download