**Simulation Plan**

Tripartite Simulation Subteam

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1. **Foundational Elements**

***Treatment Discontinuation***

We want to study various missingness scenarios. By “missing data” we mean data that was described to be collected in the protocol (as if all randomized patients adhered and completed the protocol), but are not available for any reason – e.g., death, lost-to-follow-up – or are irrelevant due to substantial disruptions in the protocol defined procedures (including treatment) that confound or obscure a meaningful measure of the primary efficacy outcome - e.g., an intercurrent event.

Our efforts will be on estimating the direct treatment effect; that is, the effect of **the investigational product** (or experimental medication, denoted X) that is being developed by the Sponsor. Our primary focus will be on missing data due to discontinuation of the **randomized study medication** **(RSM).** Randomized study medications will be denoted X (experimental, investigational product), P (placebo control) and A (active/approved comparator).

Discontinuation (DC) of the RSM, and thus missing data in this sense, can occur for three primary reasons:

1. DC due to adverse events (DCAE)
2. DC due to lack of efficacy (DCLoE)
3. DC due to administrative reasons (DC Adm) (e.g., moved out of town, family matters, trial fatigue).

DC due to administrative reasons should occur completely at random, and therefore will not be studied in detail. We will merely use a constant rate of DCAdm across all simulations.

The following table displays a wide range of missingness patterns due to DCAE and DCLoE.

<Note that this is from past TWT Meeting Minutes dated 20 Aug 2021, and can be updated or changed as we see fit.>

|  |  |  |
| --- | --- | --- |
| **Scenarios** | **Placebo Discontinuation Rates** | **Treatment Discontinuation Rates** |
| 1 | 2% AE; 8% LoE | 0% AE; whatever happens for LoE |
| 2 | 5% AE; 20% LoE | 0% AE; whatever happens for LoE |
| 3 | 8% AE; 32% LoE | 0% AE; whatever happens for LoE |
|  |  |  |
| 4 | 0% AE; whatever happens for LoE | 8% AE; 2% LoE |
| 5 | 0% AE; whatever happens for LoE | 20% AE; 5% LoE |
| 6 | 0% AE; whatever happens for LoE | 32% AE; 8% LoE |

1. Hege / Hakeem Update

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Placebo | | | |
| Treatment | 0% | 10% | 25% | 40% |
| 0% | Complete Data | 2% AE; 8% LoE | 5% AE; 20% LoE | 8% AE; 32% LoE |
| 10% | 8% AE; 2% LoE |  |  |  |
| 25% | 20% AE; 5% LoE |  |  |  |
| 40% | 32% AE; 8% LoE |  |  |  |

We can refine this more if needed (e.g., 10%, 15%, 20%, 25%).

Hakeem Hege

**Hege’s Results Summary**

|  |  |  |
| --- | --- | --- |
| **Scenarios** | **Placebo Discontinuation Rates** | **Treatment Discontinuation Rates** |
| 1 | 2.0% AE; 8.4% LoE | 0% AE; 4.2% LoE |
| 2 | 5.4% AE; 20.3% LoE | 0% AE; 12.5% LoE |
| 3 | 8.1% AE; 32.2% LoE | 0% AE; 22.7% LoE |
|  |  |  |
| 4 | 0% AE; 4.8% LoE | 8.0% AE; 2.2% LoE |
| 5 | 0% AE; 9.0% LoE | 20.4% AE; 5.3% LoE |
| 6 | 0% AE; 13.5% LoE | 31.7% AE; 8.0% LoE |

Having DC due to LoE for placebo necessarily induces DC for LoE on treatment.

The goal is to fill in the scenarios depicted in the table above. This will provide a wide range of DC patterns across Treatment and Control/Placebo from which we can explore different estimands and different estimators for those estimands.

***Null and Alternative Hypotheses***

We want to study the performance of various estimators for the defined estimands under the null hypothesis and at least two alternative hypotheses. Here it is important to define a “null scenario” and distinguish it from a “null hypothesis.”

We will refer to a “null scenario” as one in which the underlying multivariate normal means for both X and P (or A) are the same, and without loss of generality, both equal to zero. So, the difference in the means is zero or “null.” However, due to RSM discontinuation and any assumptions or defined modeling approaches as well as the definition of an estimand, the true treatment effect (difference in the true means of X and P/A) in that scenario may create a non-zero difference. For example, if one were to define an estimand based on the principal stratum of patients who would adhere to either RSM, the true mean response on X and the true mean response on P/A may not be zero since those adhering to their RSM may be more favorably disposed to a beneficial effect of their RSM. Furthermore, the mean responses on X and P/C may be different, thereby creating a non-zero treatment effect. The estimand framework has helped to highlight this phenomena, though it is under-appreciated.

So, for this simulation study we will identify “scenarios” in which we know the underlying mean response for each RSM, and we will examine what that means in terms of the true treatment effect for assessing unbiased estimation and hypothesis testing.

Scenarios

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Scenarios - Means for Treatment Response Assuming Complete Data** | | | |
|  | Null | Small | Medium | Large |
| Investigational Product / Experimental Medication | 0 | 0.5 | 1 | 2 |
| Placebo /  Active Comparator | 0 | 0 | 0 | 0 |

***Sample Size***

Different estimation methods require assumptions and some depend on asymptotic theory so it is meaningful to assess their performance under finite samples sizes that may be encountered in clinical trials. We will examine small, medium and large clinical trials correspoinding toearly Phse 2 studies, late Phase 2 studies and Phase 3 studies.

N = 100, 200, 500 patients/treatment (we can discuss whether these are the right numbers of not)

***Primary Outcome Variable***

We will focus solely on continuous outcomes for now (e.g., multivariate normal distributions). Future work can incorporate binary outcomes.

***Data Generation***

We will use the CITIES tool. WE can explore MAR and MNAR assumptions for the underlying data and evaluate estimands and estimators under those assumptions.

1. **Evaluation**

***The Estimand***

We will first define the estimands of interest. For the scope of this work, we will study the most popular ones in practice today.

1. The initiation of treatment estimand (corresponds to ITT – the effect of initiating treatment)
2. The hypothetical estimand (the effect of treatment if everyone cold indeed adhere to the RSM). Note that this is targeting the multivariate normal means underlying the data generating model.
3. The Adherers Average Causal Effect (AdACE) – the treatment effect in those who can adhere to their RSM.
   1. S\*+
   2. S++

We will first simulate data under the null scenario (i.e., multivariate normal means of zero), and produce 10,000 simulations as a way to approximate (quite accurately) the true mean response for each RSM and the treatment effect, i.e., the estimand, the target of estimation. This can be done for the various treatment discontinuation patterns and missingness assumptions (MAR, MNAR). It is not dependent on sample size.

I think this could be very enlightening.

***The Estimators***

For each estimand, we can define different estimators and analysis approaches. Some proposals are listed here, but need more discussion and definition:

1. Intention to Treat – there are some problems with this but too many to describe here … yet.
2. MMRM
3. Other longitudinal models / competitors to MMRM (if we want to pursue those)?
4. AdACE (Qu et al)
5. DIA SAS macro (Rubin extension method?)

Assess bias and coverage

Note that bias could be construed as difference from the true estimand mean and I will call it pseudo-bias, the difference from the multivariate normal mean.

The same can be said for coverage probability.

Assess power

As a function of increasing difference in multivariate normal means