
Estimands in Huntington's Disease
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Huntington's Disease (HD)

- HD is a genetic (autosomal-dominant, monogenic and fully penetrant), neurodegenerative and ultimately fatal disease characterized by a range of cognitive, behavioral and motor symptoms.
- Caused by a cytosine-adenine-guanine (CAG) trinucleotide repeat expansion in huntingtin protein (HTT) coding gene.
- The estimated prevalence of HD ranges from 5.96 to 13.17 cases per 100,000.
- Median survival is ~15 years from onset of motor symptoms (typically ~45 years of age)
- Higher mutant CAG repeat size and older age are associated with a faster rate of disease progression
- Currently there is no approved treatment in slowing down/reverse the disease progression in HD.

GENERATION HD1

- A randomized, double-blind, double-dummy, placebo-controlled trial in manifest Huntington's disease.
- Trial objective –
 - To evaluate the efficacy of the Tominersen (RG6042) compared with placebo in patients diagnosed with manifest HD, as measured by change from baseline in the composite Unified Huntington's Disease Rating Scale (cUHDRS) at Week 101.

Challenges in the HD

- No well-established primary endpoint in HD – no approved disease modifying treatment.
 - Only Tetrabenazine approved in treating HD for chorea symptoms.
- Within manifest HD population, no clear definition for the disease progression.
 - Limitation in choice of endpoints: challenge to consider time-to-event endpoint.
- Definition of intercurrent events
 - Challenges in anticipating all possible ICEs unique to the underlying population due to limited experience in HD.
 - Withdrawal rate, rate of starting symptomatic treatment
- Need to closely collaborate with the Health Authorities to overcome those challenges.
 - Choice of endpoint, defining the targeted population, use of relevant biomarkers.

Estimand attributes

- **Treatment:**
 - 120mg Tominersen bi-monthly
 - 120mg Tominersen every 4 month administration (with alternating placebo)
 - Placebo bi-monthly
- **Population:** Manifest HD patients
- **Primary Endpoint**
 - Composite Unified Huntington's Disease Rating Scale at Week 101
- **Intercurrent Events**
 - Withdraw from Treatment
 - Death
- **Population level summary:** The difference in mean change from baseline between the active treatment and placebo at Week 101

Handling of Intercurrent Events

- **Withdraw from Treatment**

- *Due to Treatment and/or Disease Progression Related reasons (TDPR) -> **Treatment Policy***
 - the actual observed “off-treatment” values will be analyzed.



Handling of Intercurrent Events

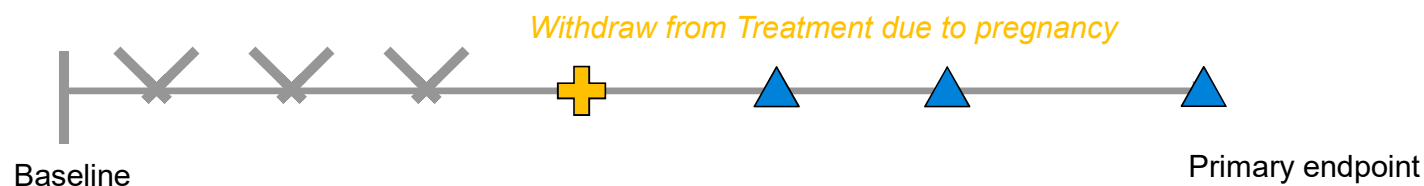
- **Withdraw from Treatment**

- *Due to Treatment and/or Disease Progression Related reasons (TDPR) -> **Treatment Policy***
 - the actual observed “off-treatment” values will be analyzed.



- *Due to Non-Treatment or Disease Progression Related reasons (NTDPR) **hypothetical strategy***

- Discard the actual observed “off-treatment” values and imputed by hypothetical values as if patients had continued receiving the study treatment.

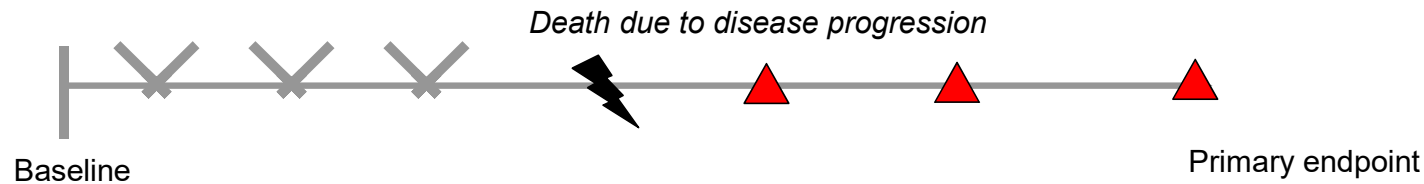


Handling of Intercurrent Events

- **Death –**

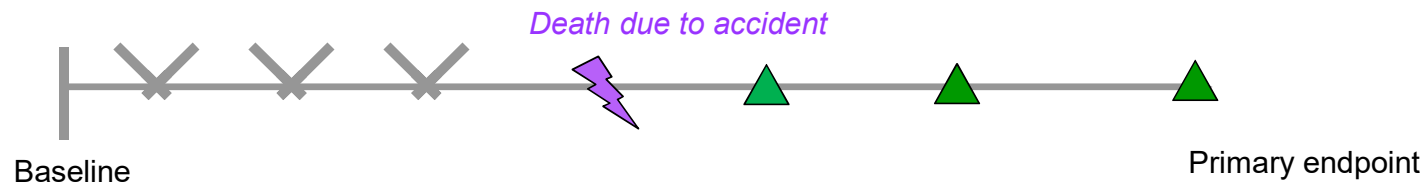
- *Due to TDPR -> Hypothetical Strategy*

- Imputed by placebo patients as if the patients had discontinued from the treatment.



- *Due to NTDPR -> Hypothetical Strategy*

- Imputed within the same treatment group as if the death had not occurred and patients continued on the assigned treatment.

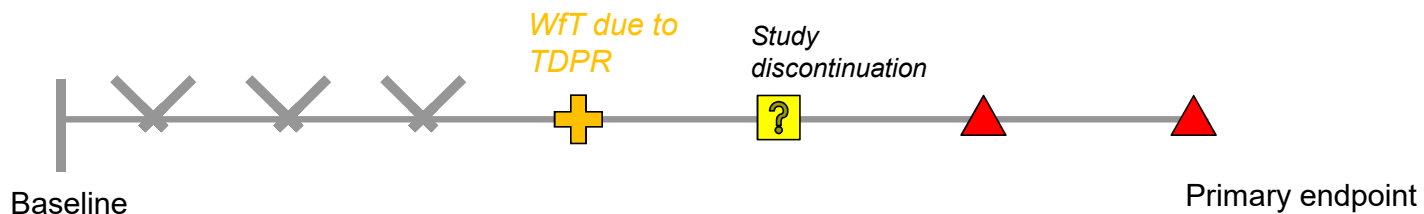


Missing Data

- Per protocol design, patients who withdraw from treatment, if not withdraw from study, will return for 3 follow-up visits including the primary endpoint Week 101

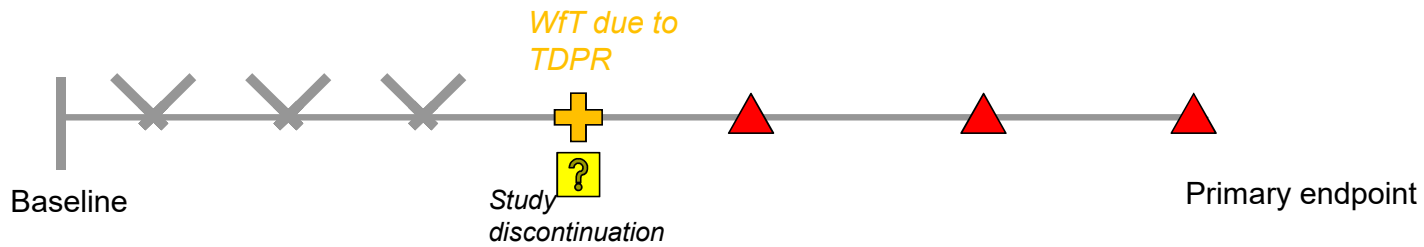
Handling of Missing Data

- Per protocol design, patients who withdraw from treatment, if not withdraw from study, will return for 3 follow-up visits including the primary endpoint Week 101
 - Scenario 1 –
 - If patients WfT due to TDPR and fail to return or WfS later, missing values will be imputed by observed values from placebo patients

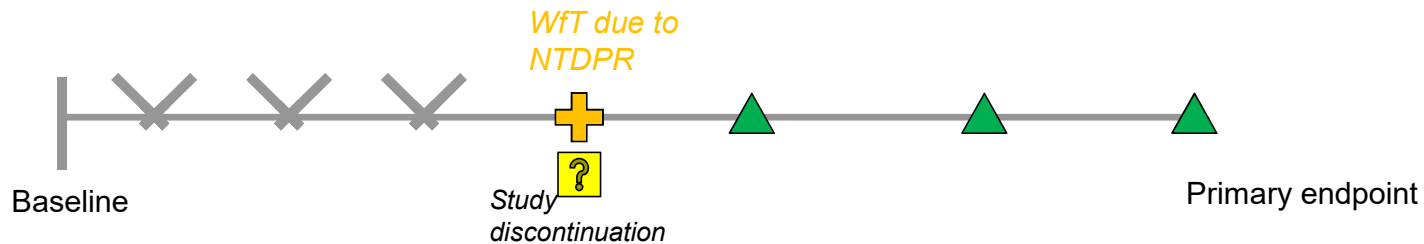


Handling of Missing Data

- Scenario 2: WfT triggers WfS – both events occurred on the same date.
 - If any of the reasons is due to **TDPR**, missing data will be imputed by observed values from placebo patients



- both due to **NTDPR**, missing data will be imputed **within each treatment group**.



Data Handling Methods

Handling Rules	Intercurrent Events	Missing data
Observed data included in the analysis	<ul style="list-style-type: none"> Withdraw from Treatment due to TDPR (Treatment Policy) 	--
Imputed by placebo	<ul style="list-style-type: none"> Death due to TDPR (Hypothetical strategy) 	<ul style="list-style-type: none"> Missing data after the WfT due to TDPR
Imputed within treatment group	<ul style="list-style-type: none"> WfT due to NTDP (Hypothetical Strategy) Death due to NTDP (Hypothetical Strategy) 	<ul style="list-style-type: none"> Intermediate (i.e. non monotonic) missing

Categorization of WfT/WfS reasons to TDPR vs NTDPR?

- The withdrawal reasons are collected via eCRF.
 - Tick box, e.g. lack of efficacy, adverse events, physician's decisions.
 - Free text field are mandated.
- Study team review the reasons periodically and determine if it's TDPR/NTDPR.
 - If vague, the query would be raised to the investigators for further clarifications.
 - Clinical operations to contact with the sites to understand the process leading to withdrawal.
 - If ambiguity remains, assigned to TDPR as a conservative approach.
 - The categorization will be finalized and documented prior to the unblinding of the study.

Supplementary Estimands

- The primary estimand combines “treatment policy” and “hypothetical strategy” to handle ICEs
- **Supplementary Estimand 1 - pure treatment policy**
 - *Objective: To evaluate the treatment effect in a real-world setting where patients may discontinue from the treatment and lose any treatment benefit.*
 - All other attributes remain the same
 - Pure “treatment policy” only for handling ICE
 - All withdrawal from treatment or death are due to TDPR.
 - Include observed data in the analysis and if missing, imputed by observed values from placebo patients.

Supplementary Estimands

- **Supplementary Estimand 2 – pure hypothetical strategy**
 - *Objective: To evaluate the treatment effect as if all patients adhere to the planned treatment and study protocol.*
 - All other attributes remain the same
 - Pure “hypothetical strategy” only for handling ICE
 - Mixed model repeated measurements (MMRM) will be applied. Hypothetical values are imputed under missing at random assumption.

Summary

- Estimand framework provides a structural approach to aligning a trial objective with the study design, including endpoints, primary analysis, sensitivity analysis, sample size considerations and data collection.
- The definition of ICE helps to delineate from the missing data problem when outlining the analysis strategy.
- Facilitate the communication with the broader team when emphasizing the importance of minimizing missing data and collecting the withdrawal reasons/following-up patients.
- Knowledge of disease area and precedence with HAs approval helps in defining the estimand strategy
 - In HD, both limited experience with HD and lack of approved drugs --> a sensible estimand strategy need to be designed from scratch.

Thank you for your attention!

Doing now what patients need next