Power Assessment for Hierarchical Combination Endpoints Using Joint Modelling of RTTE and TTE Models versus Finkelstein-Schoenfeld Method
Transthyretin Amyloidosis (ATTR)

- Transthyretin (TTR) is a circulating plasma protein that normally exists as a stable homotetramer. In diseased patients an unstable tetramer structure leads to formation of amyloid fibrils and subsequent tissue deposition in organs/tissues.

- Two distinct clinical presentations of the amyloidosis: transthyretin familial amyloid polyneuropathy (ATTR-FAP) when the peripheral nerves are primarily affected and transthyretin amyloid cardiomyopathy (ATTR-CM) when the heart is primarily affected.

- ATTR-CM is a late onset disease and is rarely diagnosed. Death in most patients with cardiomyopathy is from cardiac causes, including sudden death, heart failure, and myocardial infarction.
It’s a RARE Disease

- Cardio-vascular trial sample size ~10 000 - 20 000 patients
It’s a RARE Disease

- Cardio-vascular trial sample size ~10,000 - 20,000 patients

“Approximately 800-1000 diagnosed patients with ATTR-CM worldwide.”¹

n = ~ 400 available

¹ Ando Y et al. Guideline of transthyretin-related hereditary amyloidosis from clinicians. Orphanet Journal of Rare Diseases. 2013;8:31
It’s a RARE CARDIO-VASCULAR Disease

- Cardio-vascular trial sample size ~10 000 - 20 000 patients

Survival is the golden standard CV-related endpoint:

Low power to detect drug effect with the available sample size, too long to show benefit alone

Hence, use of an ancillary longitudinal endpoint:

*Frequency of cardiovascular-related hospitalization visits*
Objectives

- Compare power performances to detect a (small) drug effect for the purpose of informing a dose recommendation for a rare disease
  - Apply the non-parametric Finkelstein-Schoenfeld (FS) test
  - Enhance trial analytical metric with a model-based approach
    - Exposure - Time-to-Event (TTE) for survival data
    - Exposure - TTE with hospitalization frequency as time-varying covariate (TTE-COV)
    - Exposure - Repeated Time-to-Event (RTTE) for hospitalization frequency
    - Joint Exposure Repeated Time-to-Event and Time-to-Event (Joint RTTE+TTE)
Methodology Framework – Assumptions

**Trial design:**
30 months
2:1:2, n=400
Placebo: low: high

**Hazard Distributions:**
1) Exponential for mortality and HO
   \( h(t) = \lambda \)
2) Exponential for mortality and Weibull for HO
   \( h(t) = \lambda \alpha (\lambda \cdot t)^{\alpha - 1} \)
3) 40% no event

**Correlation between hazards:**
1) \( R^2 = 0 \)
2) \( R^2 = 1 \)

**Treatment Effect Size:**
- 15% mortality
- 0.5 CV-related HO for **high** dose

**Power versus sample size**

**PK, mortality, hospitalization (HO) data**

- FS
- TTE
- TTE-COV
- RTTE
- RTTE + TTE

Type I error
Convergence

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Prior regulatory history in cardiac medical device trials \(^3,4\)

- Non-parametric **hierarchical** & **pairwise** test derived from patient-to-patient comparison

\[ \begin{array}{ccccc}
\text{Black and grey died} & 0 & -1 & -1 & -1 \\
\text{Only black died} & +1 & 0 & +1 & \\
\text{Only grey died} & +1 & 0 & +1 & \\
\text{Both died} & -1 & -1 & 0 & -1 \\
\text{Both alive} & 1+ & & +1 & 0 \\
\end{array} \]

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Prior regulatory history in cardiac medical device trials

Non-parametric hierarchical & pairwise test derived from patient-to-patient comparison

1) Black and grey died but...
2) Black died before grey
Finkelstein-Schoenfeld (FS)

- Prior regulatory history in cardiac medical device trials
- Non-parametric **hierarchical** & **pairwise** test derived from patient-to-patient comparison

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Finkelstein-Schoenfeld (FS)

- Prior regulatory history in cardiac medical device trials
- Non-parametric hierarchical & pairwise test derived from patient-to-patient comparison

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\begin{array}{c|c|c|c|c|c}
\text{Patient} & \text{Patient} & \text{Patient} & \text{Patient} & \text{Patient} \\
\hline
+1 & 0 & -1 & -1 & -1 \\
+1 & 0 & +1 & 0 & +1 \\
+1 & -1 & -1 & 0 & -1 \\
+1 & +1 & 0 & 0 & 0 \\
\end{array}
\]
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<td>+1</td>
<td>-1</td>
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<td>0</td>
<td>-1</td>
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Prior regulatory history in cardiac medical device trials

Non-parametric hierarchical & pairwise test derived from patient-to-patient comparison
Finkelstein-Schoenfeld (FS)

- Prior regulatory history in cardiac medical device trials
- Non-parametric hierarchical & pairwise test derived from patient-to-patient comparison

In each stratum:

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<tr>
<th></th>
<th>0</th>
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<th>-1</th>
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<th>( U_i )</th>
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<tbody>
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<td>+1</td>
<td>0</td>
<td>+1</td>
<td>+1</td>
<td>+1</td>
<td>+4</td>
</tr>
<tr>
<td>2</td>
<td>+1</td>
<td>-1</td>
<td>0</td>
<td>+1</td>
<td>-1</td>
<td>0</td>
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<tr>
<td></td>
<td>+1</td>
<td>-1</td>
<td>-1</td>
<td>0</td>
<td>-1</td>
<td>-2</td>
</tr>
<tr>
<td></td>
<td>1+</td>
<td>-1</td>
<td>+1</td>
<td>+1</td>
<td>0</td>
<td>+2</td>
</tr>
</tbody>
</table>

\[ H \]
Finkelstein-Schoenfeld (FS)

- Prior regulatory history in cardiac medical device trials
- Non-parametric hierarchical & pairwise test derived from patient-to-patient comparison

\[
\sum U_i \\
\sum U_i
\]

Active

Generalized Gehan Wilcoxon test

Placebo

\[
\begin{array}{cccccc}
& \pm & + & - & 1 & 0 \\
\pm & 0 & -1 & -1 & -1 & -1 & -4 \\
+ & 1 & 0 & +1 & +1 & +1 & +4 \\
+ & 1 & -1 & 0 & +1 & -1 & 0 \\
+ & 1 & -1 & -1 & 0 & -1 & -2 \\
+ & 1 & -1 & +1 & +1 & 0 & +2 \\
\end{array}
\]

\[p\text{-value}\]
Results: FS U-score distributions

Waterfall plot for U scores stratified by Survival

Kaplan-Meier equivalent

No TTE event
Results: FS U-score distributions

Waterfall plot for U scores stratified by HO frequency

- HO ignored
- Improvement in FS
- Kaplan-Meier equivalent
- No HO event
Drawbacks with Finkelstein-Schoenfeld

- FS maintains the hierarchy (Mortality > HO), but
  - Ignores the assessment of the HO endpoint in patients who die in the trial

- FS ignores the longitudinal aspect of the events
  - Drop-out if it’s a competitive risk to death or dose interruption not accounted for

- FS cannot test a dose-response if more than 1 active group
  - Differentiation of doses requires multiple subgroup comparisons

- FS is based on fixed set of strata (ie. categorical covariates)
  - Integration of continuous covariates only if categorized
  - Smaller N in each stratum to perform the test
**Joint RTTE + TTE**

- Shared random effects (log-normal)
- Link function as an estimated scaling factor (on baseline and/or on shape)
- $MIX$ to have 40% of the population without an event
- DRUG effect = Emax reduction on the baseline hazard of RTTE/TTE (and/or shape of Weibull)
- One-inflated negative binomial for hospitalization duration
Joint RTTE + TTE

- Shared random effects (log-normal)
- Link function as an estimated scaling factor (on baseline and/or on shape)
- $\text{MIX to have 40\% of the population without an event}$
- DRUG effect = Emax reduction on the baseline hazard of RTTE/TTE (and/or shape of Weibull)
- One-inflated negative binomial for hospitalization duration
Results: Scenario A - similar placebo/low dose

<table>
<thead>
<tr>
<th>Method</th>
<th>FS</th>
<th>TTE</th>
<th>TTE-COV</th>
<th>RTTE</th>
<th>Joint RTTE+TTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power *(%)</td>
<td>10</td>
<td>27 (77%)</td>
<td>23 (69%)</td>
<td>75 (90%)</td>
<td>79 (93%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Method</th>
<th>FS</th>
<th>TTE</th>
<th>TTE-COV</th>
<th>RTTE</th>
<th>Joint RTTE+TTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power *(%)</td>
<td>37</td>
<td>29 (77%)</td>
<td>42 (76%)</td>
<td>42 (60%)</td>
<td>65 (95%)</td>
</tr>
</tbody>
</table>

* Convergence in brackets
Results: Scenario B - similar low/high dose

<table>
<thead>
<tr>
<th>Method</th>
<th>FS</th>
<th>TTE</th>
<th>TTE-COV</th>
<th>RTTE</th>
<th>Joint RTTE+TTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power *(%)</td>
<td>17</td>
<td>20</td>
<td>19 (62%)</td>
<td>71 (83%)</td>
<td>70 (83%)</td>
</tr>
</tbody>
</table>

* Convergence in brackets
Results: Scenario C – Emax relationship

<table>
<thead>
<tr>
<th>Method</th>
<th>FS</th>
<th>TTE</th>
<th>TTE-COV</th>
<th>RTTE</th>
<th>Joint RTTE+TTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power <em>(%)</em></td>
<td>13</td>
<td>20 (77%)</td>
<td>23 (63%)</td>
<td>61 (86%)</td>
<td>62 (94%)</td>
</tr>
</tbody>
</table>

Method: FS, TTE, TTE-COV, RTTE, Joint RTTE+TTE

* Convergence in brackets
### Results: All scenarios type I error rates

<table>
<thead>
<tr>
<th>Correlation</th>
<th>Endpoint</th>
<th>Method</th>
<th>Type I* (%)</th>
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</thead>
<tbody>
<tr>
<td><strong>R² = 1</strong></td>
<td><strong>Mortality HO data</strong></td>
<td>FS</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td><strong>Mortality data only</strong></td>
<td>TTE</td>
<td>4 (43%)</td>
</tr>
<tr>
<td></td>
<td><strong>Mortality HO data</strong></td>
<td>TTE-COV</td>
<td>7 (45%)</td>
</tr>
<tr>
<td></td>
<td><strong>HO data only</strong></td>
<td>RTTE</td>
<td>7 (58%)</td>
</tr>
<tr>
<td></td>
<td><strong>Mortality HO data</strong></td>
<td>Joint TTE+TTE</td>
<td>2 (57%)</td>
</tr>
<tr>
<td><strong>R² = 0</strong></td>
<td><strong>Mortality HO data</strong></td>
<td>FS</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td><strong>Mortality data only</strong></td>
<td>TTE</td>
<td>2 (30%)</td>
</tr>
<tr>
<td></td>
<td><strong>Mortality HO data</strong></td>
<td>TTE-COV</td>
<td>3 (32%)</td>
</tr>
<tr>
<td></td>
<td><strong>HO data only</strong></td>
<td>RTTE</td>
<td>4 (37%)</td>
</tr>
<tr>
<td></td>
<td><strong>Mortality HO data</strong></td>
<td>Joint TTE+TTE</td>
<td>2 (17%)</td>
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</table>

* Convergence in brackets
Summary

- Implementation of a model-based approach to link the probability of survival and the probability of hospitalization events.

- In general, the joint RTTE+TTE and the RTTE methods provided the highest power to detect a drug effect.
  - While correlated, the gain of power from the joint RTTE+TTE model is very moderate.
  - While uncorrelated, the joint RTTE+TTE model added extra power by acknowledging the additional information from the TTE data.
  - FS results were superior to TTE alone in general, but vary across the scenarios.
  - Type I error rates were controlled in general and convergence rates with an Emax model show adequate robustness of the models in power assessment.

- Challenges in introducing drug effects and characterizing the underlying relationship if multiple confounders exist. In case of informative dropout, a dropout model can be implemented but may be competitive to mortality.

- Hierarchical metrics in power assessment could mimic FS decision rules.

- Smaller sample sizes to detect a treatment effect in future trials could be achieved using this methodology.
Acknowledgment

- Jeffrey H Schwartz
- Balarama Gundapaneni
- Daniel Meyer
- Steve Gibbs
- Ken Salatka
- Crima Shah
- Vijayakumar Sundararajan
- Tim Nicholas
- Yea Min Huh
- Sridhar Duvvuri
- Jae Eun Ahn
- Chay Lim

And:

Rare disease patients in the study