Selecting the primary endpoint in a randomized clinical trial. A cardiovascular case study

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Outline and goals

1. Randomized Clinical Trials, Composite Endpoints and Motivation
2. Statistical methodology
3. **CompARE**: Web-based platform to help in the decision between CE or a component as the primary endpoint
4. Case study from cardiovascular area
5. Further research
Randomized Clinical Trial - Scheme

TOTAL PATIENTS (Population) → Sample

Control treatment → PRIMARY ENDPOINT

New treatment → PRIMARY ENDPOINT

Sample → Randomized allocation

TOTAL PATIENTS (Population) → Sample

Control treatment

New treatment

Follow-up
Randomized Clinical Trial - Scheme

- **Total Patients (Population)**
- **Sample**
- **Randomized allocation**
- **Control treatment**
- **New treatment**
- **Follow-up**

**Dilemma?**

- **Composite endpoint**
  (Death + Stroke)
- **A component**
  (Death)

**Primary Endpoint**

Studies involving Composite endpoints

- **ARISE**\(^{(1)}\) trial:
  - Control group \((n = 3066)\)
  - Succinobucol \((n = 3078)\)

Studies involving Composite endpoints

- **ARISE**\(^{(1)}\) trial:
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  - Succinobucol \((n = 3078)\)

  **Relevant Endpoint**
  - CV death
  - Myocardial infarction
  - Stroke
  - Res. cardiac arrest

  **Additional Endpoint**
  - Hospitalization

  **Composite Endpoint**
  (Chosen as primary)

<table>
<thead>
<tr>
<th>Control</th>
<th>Treat.</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.2%</td>
<td>6.7%</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Control</th>
<th>Treat.</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.4%</td>
<td>11.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Control</th>
<th>Treat.</th>
</tr>
</thead>
<tbody>
<tr>
<td>17%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Clinical Trials and Composite endpoints

The ARE method

CompARE

Extensions of CompARE

Studies involving Composite endpoints

- **ARISE**: trial:
  - Control group ($n=3066$)
  - Succinobucol ($n=3078$)

- **LIFE**: study:
  - Control group ($n=4588$)
  - Losartan ($n=4605$)

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Composite endpoints

Clinical concerns
- Medical meaning of the composite
- Relevance with the objectives of the study
- Similar expected effects on each component

Statistical concerns
- Address the problem of multiple comparisons
- Avoid bias due to competing risks
- We observe a higher number of occurrences
Composite endpoints

Clinical concerns

- Medical meaning of the composite
- Relevance with the objectives of the study
- Similar expected effects on each component

Statistical concerns

- Address the problem of multiple comparisons
- Avoid bias due to competing risks
- We observe a higher number of occurrences and CAN (but not always)
- Reduce sample size
- Increase power
Some notation

Composite endpoints $\mathcal{E}_*$ are defined as the union of a given set of events $\mathcal{E}_1, \ldots, \mathcal{E}_n$.

$$\mathcal{E}_* = \mathcal{E}_R \cup \mathcal{E}_A.$$  

$T_R, T_A$ time to $\mathcal{E}_R, \mathcal{E}_A$.

$T_* = \min\{T_R, T_A\}$.

$HR_R, HR_A$ treatment effect of $\mathcal{E}_R, \mathcal{E}_A$.

$p_R, p_A$ probability of observing $\mathcal{E}_R, \mathcal{E}_A$ in control group.
Survival Analysis and the Logrank test

- **Relevant endpoint**

  \[ H_0 : HR_R = 1 \]
  \[ H_1 : HR_R,n(t) = e^{g(t)} / \sqrt{n} \] (*)&

  Logrank Test Statistic \( Z_R \):
  \[ Z_R \sim N(0, 1) \text{ under } H_0 \]
  \[ Z_R \sim N(\mu_R, 1) \text{ under } H_1 \]

- **Composite endpoint**

  \[ H_0 : HR_\ast = 1 \]
  \[ H_1 : HR_\ast,n(t) = e^{g_\ast(t)} / \sqrt{n} \]

  Logrank Test Statistic \( Z_\ast \):
  \[ Z_\ast \sim N(0, 1) \text{ under } H_0 \]
  \[ Z_\ast \sim N(\mu_\ast, 1) \text{ under } H_1 \]

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The Asymptotic Relative Efficiency (ARE)

\[ \text{ARE}(Z_*, Z_R) = \left( \frac{\mu_*}{\mu_R} \right)^2 = \frac{\left( \int_0^1 \log \left\{ \frac{\lambda_{(1)}(t)}{\lambda_{(0)}(t)} \right\} f_{(0)}(t) dt \right)^2}{(\log \text{HR}_R)^2 \left( \int_0^1 f_{(0)}(t) dt \right) \left( \int_0^1 f_R(t) dt \right)} \] (1)
The Asymptotic Relative Efficiency (ARE)

\[
\text{ARE}(Z_*, Z_R) = \left( \frac{\mu_*}{\mu_R} \right)^2 = \frac{\left( \int_0^1 \log \left\{ \frac{\lambda_*^{(1)}(t)}{\lambda_*^{(0)}(t)} \right\} f_*(0)(t) dt \right)^2}{(\log \text{HR}_R)^2 \left( \int_0^1 f_*(0)(t) dt \right) \left( \int_0^1 f_R^*(0)(t) dt \right)}
\]  \hspace{1cm} (1)

Required parameter values to calculate ARE

Assuming Weibull distributions for \( T_R, T_A \) and a Frank’s copula relationship between \( T_R, T_A \):

- \( \text{HR}_R \) and \( p_R \).
- \( \text{HR}_A \) and \( p_A \).
- \( \rho \): Spearman’s coefficient between \( T_R \) and \( T_A \).

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The Asymptotic Relative Efficiency (ARE)

- Relationship between ARE and sample sizes to achieve the same power:
  \[
  \text{ARE}(Z_*, Z_R) = \frac{n_R}{n_*} \quad (2)
  \]

---


The Asymptotic Relative Efficiency (ARE)

- Relationship between ARE and sample sizes to achieve the same power:
  \[
  \text{ARE}(Z_*, Z_R) = \frac{n_R}{n_*}
  \]  
  \(2\)
- When \(\text{ARE}(Z_*, Z_R) > 1 \Rightarrow \) the composite endpoint should be used.

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CompARE interface

- Free and easy to use (based on free software *Tiki*)
- Knowledge of R not needed (*pluginR* included)
- Accessible anywhere (laptop/mobile/tablet)
- Compatible with any operating system and browser
- Complete users’ guide documentation
CompARE interface

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**USER**

Web interface

Input information (HTML forms)

Results shown in the Web

Information processed in the server

CompARE

http://composite.upc.edu/CompARE

Execution of R code (plugin R)

Internal results saved in trackers
### Data from LIFE study (Losartan treatment)

#### Information about all the candidate endpoints for your trial

(You can modify the parameter values and run it again)

<table>
<thead>
<tr>
<th>Candidate endpoint</th>
<th>Terminating? (click if yes)</th>
<th>Probability of observing E in control group</th>
<th>Hazard Ratio</th>
<th>Type of endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV mortality</td>
<td>☑️</td>
<td>0.05</td>
<td>0.89</td>
<td>Relevant component</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>□</td>
<td>0.04</td>
<td>0.99</td>
<td>Relevant component</td>
</tr>
<tr>
<td>Stoke</td>
<td>□</td>
<td>0.07</td>
<td>0.75</td>
<td>Additional component</td>
</tr>
</tbody>
</table>

#### Advanced Features (Optional)

<table>
<thead>
<tr>
<th>Shape parameter of the Weibull Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined Relevant endpoint</td>
</tr>
<tr>
<td>Combined Additional endpoint</td>
</tr>
<tr>
<td>Correlation</td>
</tr>
</tbody>
</table>
Graphical results

Graphical results

Other outputs

- Survival and Hazard Ratio functions

![Graph showing survival and hazard ratio functions](image)
Other outputs

- **Numerical results in tables**

<table>
<thead>
<tr>
<th>Fixed parameters:</th>
<th>Hazard Ratio AE</th>
<th>Correlation</th>
<th>ARE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability RE (Control group)</td>
<td>0.9</td>
<td>0</td>
<td>0.64</td>
<td>Use RE</td>
</tr>
<tr>
<td>Probability AE (Control group)</td>
<td>0.9</td>
<td>0.15</td>
<td>0.56</td>
<td>Use RE</td>
</tr>
<tr>
<td>Hazard Ratio RE</td>
<td>0.9</td>
<td>0.3</td>
<td>0.49</td>
<td>Use RE</td>
</tr>
<tr>
<td>Distribution RE</td>
<td>Increasing Hazard Rate</td>
<td>0.9</td>
<td>0.5</td>
<td>0.39</td>
</tr>
<tr>
<td>Distribution AE</td>
<td>Constant Hazard Rate (exponential)</td>
<td>0.9</td>
<td>0.7</td>
<td>0.3</td>
</tr>
</tbody>
</table>

- **Reported recommendations in text**

- **List of previous results**
Ongoing extensions

- Computations when both RE and AE include Death
- Different copulas other than Frank’s*
Ongoing extensions

- Computations when both RE and AE include Death
- **Different copulas other than Frank’s***

Concluding Remarks and Future Extensions

- Importance of choosing the Primary endpoint in a RCT
- ARE method to choose a Composite endpoint or a component as Primary
- CompARE: Useful tool for Clinicians and Researchers
Concluding Remarks and Future Extensions

- Importance of choosing the Primary endpoint in a RCT
- ARE method to choose a Composite endpoint or a component as Primary
- CompARE: Useful tool for Clinicians and Researchers

- Incorporate sample size calculations
- Possibility to change assumptions by the user (e.g. Distribution laws)
- Binary outcomes
- Improve output results (Dynamic plots)
- Feedback from national/international colleagues
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http://composite.upc.edu/CompARE
Some references

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