SAS SYSTEM FOR THE EVALUATION OF SURROGACY IN CLINICAL TRIALS

Theophile Bigirumurame
Interuniversity Institute for Biostatistics and statistical Bioinformatics University Hasselt, Belgium

SAS ACADEMIC CONFERENCE
Leuven March 3\textsuperscript{rd}, 2016

Research team

• Geert Molenberghs
• Ariel Alonso Abadi
• Wim Van der Elst
• Theophile Bigirumurame
• Marc Buyse
• Tomasz Burzykowski
• Ziv Shkedy
Definition

• **Clinical endpoint (or true endpoint)**
  – A characteristic or variable that reflects how a patient feels, functions, or survives.

• **Biomarker**
  – A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

• **Surrogate endpoint**
  – A biomarker that is intended to substitute for a clinical endpoint. It is expected to predict clinical benefit (or harm or lack of benefit or harm)

Motivation

• **Primary motivation**
  – True endpoint is rare and/or distant
  – Surrogate endpoint is frequent and/or close in time

• **Secondary motivation**
  – True endpoint might be: invasive, uncomfortable, costly,....
Examples of surrogate endpoints used in medical research

<table>
<thead>
<tr>
<th>Disease</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surrogate</td>
</tr>
<tr>
<td>Early stage cancer</td>
<td>Time to progression</td>
</tr>
<tr>
<td>Advanced cancer</td>
<td>Tumor response</td>
</tr>
<tr>
<td>HIV infections</td>
<td>CD4 counts; viral load</td>
</tr>
</tbody>
</table>

Surrogate validation

- Before its use, a surrogate has to be validated (at the individual level and trial level)
- However, no standard software available
- We propose a set of SAS macro to perform the analysis
Individual-level surrogacy validation

The individual-level surrogacy, measures the association between the potential surrogate endpoint and the clinical endpoint, adjusting for the effect of treatment across all the trials included.

Trial-level surrogacy validation

how well one can predict the treatment effect on the clinical endpoint in a future trial based on the observed association between the treatment effects on the surrogate and clinical endpoints observed in previous trials.
Assessment of surrogacy levels

- Good surrogate is expected to have $R^2$ close to 1, at both level of surrogacy.
- Confidence interval around $R^2$ should be narrow.

The surrogacy setting:

**Surrogacy question:**
can we use treatment effect on the surrogate endpoint to predict treatment effect on the true endpoint?
Different Type of endpoints

- Survival/Survival
- Normal/Normal
- Normal/Binary
- Survival/Binary

Software

1. DATA
2. SAS MACRO
3. STANDARD OUTPUT
   - Graphical outputs
   - Surrogacy measures

Per setting
Application 1

Two continuous endpoints

Case study

- Randomized, multicenter study in ophthalmology.
- Patients with age-related macular degeneration, patients progressively lose vision
- Interferon-alpha vs placebo.
- Primary endpoint: change of visual acuity at 1 year of treatment (Diff 52).
- Surrogate endpoint: change of visual acuity after 6 months of treatment (Diff 24).
- Question: does treatment improve the visual acuity?

Can we use visual acuity after 6 months as a surrogate for visual acuity after 1 year?
Surrogacy Question: trial level surrogacy

Can we use treatment effect on Diff24 to predict treatment effect on Diff52?

A: Diff24 is not predictive
B: Diff24 is predictive

Macro call

%reduc(data=surr=true, trt=center, weighted=looa, type=)

Output:
1. Exploratory plots
2. Numeric outputs
3. Surrogates measures
Exploratory plots

Numerical outputs

<table>
<thead>
<tr>
<th>Trial</th>
<th>True Lower</th>
<th>True Estimate</th>
<th>True Upper</th>
<th>Surrogate Lower</th>
<th>Surrogate Estimate</th>
<th>Surrogate Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>13395</td>
<td>-27.0499</td>
<td>-5.5000</td>
<td>16.9400</td>
<td>-16.4300</td>
<td>1.5000</td>
<td>19.4300</td>
</tr>
<tr>
<td>13740</td>
<td>-5.9838</td>
<td>1.5800</td>
<td>13.6353</td>
<td>-7.6518</td>
<td>2.1907</td>
<td>11.6949</td>
</tr>
<tr>
<td>13629</td>
<td>0.2381</td>
<td>6.0000</td>
<td>21.2381</td>
<td>5.1787</td>
<td>7.5000</td>
<td>20.1787</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Removed Trial</th>
<th>Indiv. level</th>
<th>Trial level</th>
</tr>
</thead>
<tbody>
<tr>
<td>13395</td>
<td>0.5307</td>
<td>0.0561</td>
</tr>
<tr>
<td>13390</td>
<td>0.5315</td>
<td>0.6573</td>
</tr>
<tr>
<td>13745</td>
<td>0.5278</td>
<td>0.6702</td>
</tr>
<tr>
<td>13740</td>
<td>0.5228</td>
<td>0.6547</td>
</tr>
<tr>
<td>13748</td>
<td>0.5471</td>
<td>0.6687</td>
</tr>
<tr>
<td>13750</td>
<td>0.5264</td>
<td>0.6682</td>
</tr>
<tr>
<td>13828</td>
<td>0.5333</td>
<td>0.6521</td>
</tr>
<tr>
<td>13829</td>
<td>0.5280</td>
<td>0.0518</td>
</tr>
</tbody>
</table>
Surrogacy measures

The association at individual level or individual level surrogacy = 0.5318 (0.4315, 0.6231)
The trial level surrogacy = 0.6585 (0.4695, 0.8476)
Visual acuity after 6 months is a moderate surrogate for visual acuity after 1 year

Some optional outputs
Application 2

Two survival endpoints

Case study

- Meta-analysis in oncology
- Patients with advanced ovarian cancer
- CAP (cylophosphamide + adriamycin+ cisplatin) vs CP.
- Primary endpoint: survival time
- Surrogate endpoint: progression free survival
- Question: does CAP improve the survival time?

Can we use progression free survival as a surrogate?
Surrogacy Question: trial level surrogacy

**Can we use treatment effect on progression free survival to predict treatment effect on overall survival?**

A: PFS is not predictive
B: PFS is predictive

Macro call

`%Survival(data=surr=surrind=true=trueind=true, center=true, trial=, copula=, adjustment=)`

<table>
<thead>
<tr>
<th>ID</th>
<th>TRUE</th>
<th>TRUEIND</th>
<th>Surr</th>
<th>Surrind</th>
<th>TRT</th>
<th>CENTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>404</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>524</td>
<td>1</td>
<td>160</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>419</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>213</td>
<td>1</td>
<td>233</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>569</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>816</td>
<td>1</td>
<td>636</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>317</td>
<td>1</td>
<td>137</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>378</td>
<td>1</td>
<td>144</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>917</td>
<td>1</td>
<td>86</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>403</td>
<td>1</td>
<td>56</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>483</td>
<td>1</td>
<td>45</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>62</td>
<td>1</td>
<td>62</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>13</td>
<td>550</td>
<td>0</td>
<td>353</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

Output:
1. Exploratory plot
2. Effects plot
3. Surrogates measures
The association at individual level or individual level surrogacy = 0.8711 (0.8595, 0.8826)
The trial level surrogacy = 0.8733 (0.7989, 0.9476)
PFS seems to be a good surrogate for survival time for advanced ovarian cancer
Conclusion & Discussion

- Good surrogate is expected to have $R^2$ close to 1, at both level of surrogacy.
- Confidence interval around $R^2$ should be narrow.
- Validation specific to the disease and treatment
- Surrogates allow to read out clinical trial results earlier
- The macro will be available online soon !!!