Construction of an Estimand in a Clinical Trial on Progressive Multiple Sclerosis

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Acknowledgments

• Hans Ulrich Burger.

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Multiple sclerosis (MS)

- Inflammatory and degenerative disease of human central nervous system (CNS).
- Affects around 2.5 million people worldwide.
- One of most common neurological disorders and causes of disability of young adults, especially in Europe and North America.
- Symptoms include:
  - weakness,
  - pain,
  - visual loss,
  - bowel / bladder dysfunction,
  - cognitive dysfunction.
Diagnosis and phenotypes

• Structured diagnostic criteria that rely on
  – clinical observation,
  – neurological examination,
  – brain and spinal cord MRI scans,
  – measurement of electrical activity of the brain in response to stimulus,
  – examination of cerebrospinal fluid.

• Three phenotypes: distinguished by occurrence and timing of relapses relative to disease onset and disability progression:
  – Relapsing remitting MS (RRMS),
  – primary progressive MS (PPMS),
  – secondary progressive MS (SPMS).
Diagnosis and phenotypes

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• Three phenotypes: distinguished by occurrence and timing of relapses relative to disease onset and disability progression:
  – Relapsing remitting MS (RRMS),
  – primary progressive MS (PPMS),
  – secondary progressive MS (SPMS).
• **Relapses**: these are
  - clinically different,
  - of short duration,
  - and transient.
Clinical measure of disability: EDSS

Kurtzke Expanded Disability Status Scale

- EDSS standardly used to identify progression and relapses in MS.
- **Clinically meaningful** increase:
  - 1 point if baseline EDSS ≤ 5.5,
  - 0.5 points if baseline EDSS > 5.5.

Clinically relevant endpoint

- Time to onset of **confirmed** disability progression:
  - initial progression assessment (IDP, see previous slide),
  - sustained for at least 12 weeks, based on **scheduled** visits.

- Why **confirmed**?
  - PPMS and RRMS ultimately all progress, by nature of disease.
  - But: progression needs to be differentiated from relapse.
  - Confirmation robustifies endpoint against variability in EDSS assessment.
  - Literature: in PPMS about 80% confirmation of IDPs.

- Why **scheduled**?
  - Patients experience «ups» and «downs» in the course of their disease.
  - «Downs» $\rightarrow$ more frequent, «ups» $\rightarrow$ less frequent assessments.
  - Avoid assessment bias between arms.
Time to onset of confirmed disability progression

A. Population
   Subjects targeted by the scientific question

C. Intervention effect of interest
   How potential intercurrent events are reflected in the scientific question

B. Variable
   Quantities required to address the scientific question

D. Summary measure
   On which the treatment comparison will be based
Time to onset of confirmed disability progression

1. **Population**: defined through list of in- and exclusion criteria, nothing specific to MS.

2. **Variable**: Time to onset of confirmed disability progression, defined through
   - starting date: date of randomization,
   - event date: date of IDP, if confirmed.

3. **Intervention effect of interest**:
   - Intercurrent events between randomization and IDP.
   - Intercurrent events between IDP and confirmation (actually tied to variable).

4. **Summary measure**: hazard ratio.
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Background on exemplary trial

- Some of the following considerations inspired by RCTs in the field:
  - Against placebo.
  - Double-blind.

- *Lifelong* treatment (or until withdrawal from study).

- EDSS assessed in 12 *weekly* intervals.

- Discontinuation of treatment: patients go to safety follow-up, EDSS still collected.

- Withdrawal from study: no EDSS collected anymore.

- Death: in this population, patients
  - neither expected to die from MS nor
  - due to either treatment.

- More withdrawals expected during planning, observed rates higher than assumed in sample size computations.
### Randomization → IDP

<table>
<thead>
<tr>
<th>Intercurrent event</th>
<th>Action</th>
<th>Date</th>
<th>Estimand strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation of treatment</td>
<td>Censored</td>
<td>Last EDSS assessment during treatment</td>
<td>While on treatment</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>Censored</td>
<td>Last EDSS assessment during treatment</td>
<td>While on treatment</td>
</tr>
<tr>
<td><em>Withdrawal from study</em></td>
<td>Censored</td>
<td><em>Last EDSS assessment during treatment</em></td>
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<td><em>Death</em></td>
<td>Censored</td>
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</tr>
</tbody>
</table>

- Withdrawal, death: not explicitly pre-specified, treated as discontinuation of treatment.
- Observed withdrawal pattern (trial overall): 34% in placebo, 21% in treatment arm → censoring potentially informative.
# IDP → confirmation

<table>
<thead>
<tr>
<th>Clinical event</th>
<th>Action</th>
<th>Date</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheduled confirmation</td>
<td>Event</td>
<td>IDP</td>
<td></td>
</tr>
<tr>
<td>≥ 12 weeks after IDP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No scheduled confirmation after IDP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>remains on treatment</td>
<td>Censored</td>
<td>Last EDSS assessment</td>
<td></td>
</tr>
<tr>
<td>discontinuation of treatment</td>
<td></td>
<td></td>
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<tr>
<td>loss to follow-up</td>
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<td>withdrawal from study</td>
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<tr>
<td>death</td>
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</tbody>
</table>

- Observed withdrawal pattern between IDP and confirmation (available after unblinding only!):
  - Placebo 5%,
  - treatment 2%.

- «Imputation» of events conservative? **Yes** (not getting withdrawals means event) and **no** (higher withdrawal rate in placebo!).
Conclusions

• We apply estimand framework to existing MS endpoint post-hoc, to understand how framework will help in future studies.

• If estimand framework had existed at the time – would have facilitated
  – identification and classification of intercurrent events already during protocol development,
  – would likely have helped discussion with clinicians and regulatory colleagues.

• Special feature: intercurrent events between
  – randomization and IDP and
  – IDP and confirmation.

• Definitions depend on indication: Discontinuation of treatment after IDP =
  – event for PPMS (~80% confirmation rate),
  – but censored for RRMS (~30% confirmation rate).

• Maybe informative censoring? Account for in future trials via IPCW → hypothetial estimand?
Doing now what patients need next