When Should RCTs Standardize Co-Interventions?

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Definition / Context of Co-Intervention

Defn: Post-randomization clinical care, but not necessarily evidence-based

Context: Large multi-center Phase III RCT for Acute Conditions

Examples of Co-Intervention in Acute Treatment Phase

- Maintenance of vital signs and lab values within a certain range
- Concomitant medications, procedures, and surgeries
Heterogeneity of Co-Interventions

Pre-Randomization Subject Factors

Study Treatment "Signal"

Clinician's practice
Clinical Center SOPs
Subject's Condition

Post-Randomization Factors

Subject Outcome

Co-Interventions "Noise"
a. Should we standardize co-interventions?

b. To what extent of standardization?
Example 1: CLOTS-2 Trial  
Clots in Legs or Stockings after Stroke

- **Aim:** Prevention of DVT in post-stroke immobile patients
- **Treatment:** thigh-lengths (TL) stockings vs below-knee (BK) stockings 24/7 during hospitalization (unblinded)
- **N:** 3,114
- **Sites:** 112
- **1° Outcome:** DVT on ultrasound scan at 30 days (blinded)
- **Co-intervention of interest:** anti-thrombotic drug use according to routine care (not standardized); intent to use these drugs were known prior to randomization
- **Results:** 6.3% (TL) vs 8.8% (BK), p=0.008 (signal detected)
- **Co-intervention Distribution:** 13% (TL) vs 13% (BK)

Example 2: ATACH II Trial
Antihypertensive Treatment for Acute Cerebral Hemorrhage

Step 1
• Initiation of Standard of Care SBP Reduction

Step 2
• 1:1 Randomization w/in 3 hours of symptom onset

Step 3
• Initiation of Assigned SBP Reduction (<180 or <140) (unblinded)

Step 4
• Inpatient Clinical Care

Step 5
• Follow-up at 3 mo: mRS (blinded)

• Aim: Assess effect of intensive SBP reduction on functional outcome in ICH patients
• Max N: 1,280 (to date, 1)
• Sites: 100~150
• Co-Intervention of interest: Clinical management according to the AHA Guidelines during hospitalization (max 7 days); detailed in the protocol
ATACH II Co-Intervention Monitoring

- Only certain key clinical parameters collected and data entered during hospitalization
- All baseline and inpatient data in the database reviewed by the external Independent Oversight Committee (IOC) for the first 3 subjects at each site
- Deviations → Discussions with the site; further review of random sample by IOC

*Exclude AEs, con-meds, con-procedures, central imaging
Example 3: ProTECT Trial
Progesterone for the Treatment of TBI

- **Aim**: Assess neuroprotective effect of progesterone in non-penetrating TBI patients
- **Max N**: 1,140 (to date, 220 randomized)
- **Sites**: ~25
- **Co-interventions of interest**: 13 key clinical parameters, HOURLY throughout hospitalization (max 30 days)

### Steps

1. **Step 1**
   - Patient Enrollment
2. **Step 2**
   - 1:1 Randomization w/in 4 hours of injury
3. **Step 3**
   - Initiation of Study Drug: Progesterone or Saline (blinded)
4. **Step 4**
   - Inpatient Clinical Care
5. **Step 5**
   - Follow-up to 6 months: GOS-E (blinded)
ProTECT Co-Interventions Monitoring

- Any deviation - “transgression” - is collected and data entered on the Daily Checklist CRF, DAILY
- For each type of transgression: “Yes” on the Daily Checklist CRF triggers the Transgression CRF to be data entered DAILY

<table>
<thead>
<tr>
<th>Transgressions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse oximetry O₂ saturation &lt; 90%</td>
</tr>
<tr>
<td>Arterial Blood Gas: PaO₂ &lt; 100 mmHg</td>
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<tr>
<td>Arterial Blood Gas: PaCO₂ &lt;35 or &gt;45 mm Hg</td>
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<tr>
<td>Mean Arterial Pressure: MAP &lt; 80 mmHg</td>
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<tr>
<td>Systolic BP &lt;100 mm Hg or &gt;180 mm Hg</td>
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<tr>
<td>CPP &lt;60 mm Hg. Check n/a if not measured.</td>
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<tr>
<td>Glucose &gt;180 mg/dl or &lt;80 mg/dl</td>
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<tr>
<td>Temperature &gt;38.3°C or &lt;36.0°C (96.8°F)</td>
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<tr>
<td>ICP ≥ 20 mm Hg</td>
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<tr>
<td>INR &gt; 1.4</td>
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<tr>
<td>Platelet count &lt; 75 x 10³ / mm³</td>
</tr>
<tr>
<td>Hgb &lt; 8 gm/dL</td>
</tr>
<tr>
<td>PbtO₂ &lt;15 mmHg</td>
</tr>
</tbody>
</table>
Enter any instances where the study participant’s oxygen saturation was < 90% for the previous 24 hour calendar day in the table below.

<table>
<thead>
<tr>
<th>A. Hour</th>
<th>B. Status N=Normal (complete QC and QD) A=Abnormal U= Unknown</th>
<th>C. O₂ Sat (%)</th>
<th>D. Actions taken (Check all that apply)</th>
<th>E. Specify ‘Other’ intervention</th>
</tr>
</thead>
<tbody>
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- The form has 24 rows
- Data reviewed DAILY by the Central Project Manager and the PI to determine whether they were clinically acceptable or not
ProTECT Co-Interventions Monitoring

- Effort for a Clinical Site Study Coordinator to collect and enter transgression data: **10 min ~ 20+ hours per subject**
- Central Project Manager and PI daily reviews: **15~90 min per subject**
- # transgressions: **~8,000 in 219 subjects**
- Ave # of transgression data: **2,880 per subject ⇒ 77% (range: 100 to 11,620)**

*Exclude AEs, con-meds, con-procedures, central imaging*
Thoughts on ProTECT

- How will we use all these co-intervention data?
- Will the Trial see the signal with less “noise”?
- If positive, can the Trial results be generalizable?
- Could we have considered stratifying randomization by co-intervention (like CLOTS-2)?
- Could we use EHR to transfer much of these data into the study database?
- Could we look for a smaller effect with larger N to compensate for the unequal application of co-interventions?
Summary

<table>
<thead>
<tr>
<th>Co-Intervention</th>
<th>Monitored/Collected</th>
<th>Standardized?</th>
<th>Enforced?</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLOTS-2 Anti-thrombotic use</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>ATACH II Clinical care parameters</td>
<td>Y (some)</td>
<td>Y</td>
<td>Y (moderately)</td>
</tr>
<tr>
<td>ProTECT Clinical care parameters</td>
<td>Y (OODLES)</td>
<td>Y</td>
<td>Y (strictly)</td>
</tr>
</tbody>
</table>

- Issue 1: Should we standardize co-interventions or do we rely on randomization to equalize their effect?
- Issue 2: How much do we monitor and enforce standardization?
- Consider feasibility of implementing rigid standardizations – e.g., will surgeons change their ways?
- Weigh the costs vs benefits - financial, stress/burden on trial staff
- Potential for trial fatigue – hindrance to recruitment, timely data collection and entry
Codruta Chiuza, Cassidy Conner, and Sharon Yeatts at MUSC for providing ProTECT Trial information

NIH R01 NS062778 (ProTECT Trial); and U01 NS062091 and U01 NS061861 (ATACH II Trial)