LARGE SIMPLE TRIALS:
CHALLENGES AND OPPORTUNITIES

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Disclosures

• Employed by GSK
• Views are mine alone, not necessarily those of GSK
Case for LSTs

• Trials of promising treatments with important but small to moderate effects need to be really large
• Trials that use death as endpoint can have simple follow-up and adjudication procedures
Case for LSTs (cont’d)

• Because treatment differences in direction of effect are rare, and differences in magnitude likely to be equally distributed between group,
  – LSTs can have cheap, fast simple enrollment
  – really large trials can have simple analysis

• Because busy clinicians need easy to implement regimens,
  – LSTs can have very simple interventions
Challenges + Opportunities

“Challentunities”
CHALLENGE UNITIES
FOR LSTs

• External Validity
• Treatment Heterogeneity
• Medication Safety
• Patient Reported Outcomes
Challenges for LSTs: External Validity

• LSTs designed for small treatment effect
  • is it possible that a very small benefit within LST will not have positive benefit in intended target population?

• All trials, LSTs included, involve selection criteria
  • Patients meeting those criteria may suffer fewer side-effects or have different response from overall target population
LST and External Validity: GISSI-3

Treatment for ischemic heart disease
45% of 43,047 patients admitted to CCU in participating hospitals randomized

Companion study excluded patients had roughly twice mortality of included patients

– ARR only 1.4%...therefore...

May be that small positive effect in LST trial population that is highly compliant and shows fewer immediate side-effects, has a net negative effect in target population where patients are partially compliant, have more side effects, etc.
LSTs and TREATMENT HETEROGENEITY

Analyses for variation of treatment effect
  – absence of effect heterogeneity sometimes cited as reason for LSTs
  – minimizing data collection at baseline and during follow up strength of design
• Plan for treatment heterogeneity as primary goal of research
  – collect clinical and laboratory data relevant analyses
## Table 3: Unreliability of “data-dependent” subgroup analyses

<table>
<thead>
<tr>
<th>Astrological birth sign</th>
<th>Vascular death by 1 month</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirin</td>
<td>Placebo</td>
</tr>
<tr>
<td>Libra or Gemini</td>
<td>150 (11.1%)</td>
<td>147 (10.2%)</td>
</tr>
<tr>
<td>All other signs</td>
<td>654 (9.0%)</td>
<td>869 (12.1%)</td>
</tr>
<tr>
<td>Any birth sign</td>
<td>804 (9.4%)</td>
<td>1016 (11.8%)</td>
</tr>
</tbody>
</table>

ISIS-2 trial of aspirin among over 17 000 patients with suspected acute myocardial infarction.
LSTs and Treatment Heterogeneity

• Analyses for variation in risk and response could be major advantage of LSTs
• Subgroups can be based on clinical biology, not astrology
• Requires that we plan for data collection that enables relevant analyses
LSTs and SAFETY EVALUATIONS

• Critical requirement for new medicines in pre-approval period
• Highly choreographed approach to some risks, such as hepatic, renal and QT prolongation
• Systematic approach to serious adverse events, including common ones such as hospitalization and rare ones such as Stevens-Johnson Syndrome
LSTs and Safety

When adverse events occur, detailed clinical data needed for regulatory review and clinical evaluation
PATIENT REPORTED OUTCOMES IN LSTs

• Stated advantage is use of outcomes such as death or major morbidity
  – reinforces major limitation of RCTs as currently performed

• Can LSTs retain their efficiency but expand their value for patients and physicians?
LSTs AND NEW INFORMATION TECHNOLOGIES

Designed and conducted embedded in EHR
• requires data linkages but also systematic data collection integrated in clinical practice

Conducted outside of “brick and mortar” sites
• recruitment, consent, medication, follow up all outside usual research infrastructure (Mytrus)

Incorporate methods/data of social media (PLM)
Looking Ahead

• Gretzky and the future of LSTs
• Risk of turning LSTs into LCTs (large complex trials)
• Preserve efficiency while increasing value for clinical decision making by physicians and patients
• Look to new research technologies/data