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"

CHALLENTUNITIES 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

Whimsy

Astrological birth sign	Vascular death by 1 month		p
	Aspirin	Placebo	
Libra or Gemini	150 (11·1%)	147 (10·2%)	0·5
All other signs	654 (9·0%)	869 (12·1%)	<0·0001
Any birth sign	804 (9·4%)	1016 (11·8%)	<0·0001

Table 3: **Unreliability of "data-dependent" subgroup analyse ISIS-2 trial of aspirin among over 17 000 patients with suspected acute myocardial infarction**[23]

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 INFORMATON 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