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Opportunities for Large Simple Trials – An FDA Perspective

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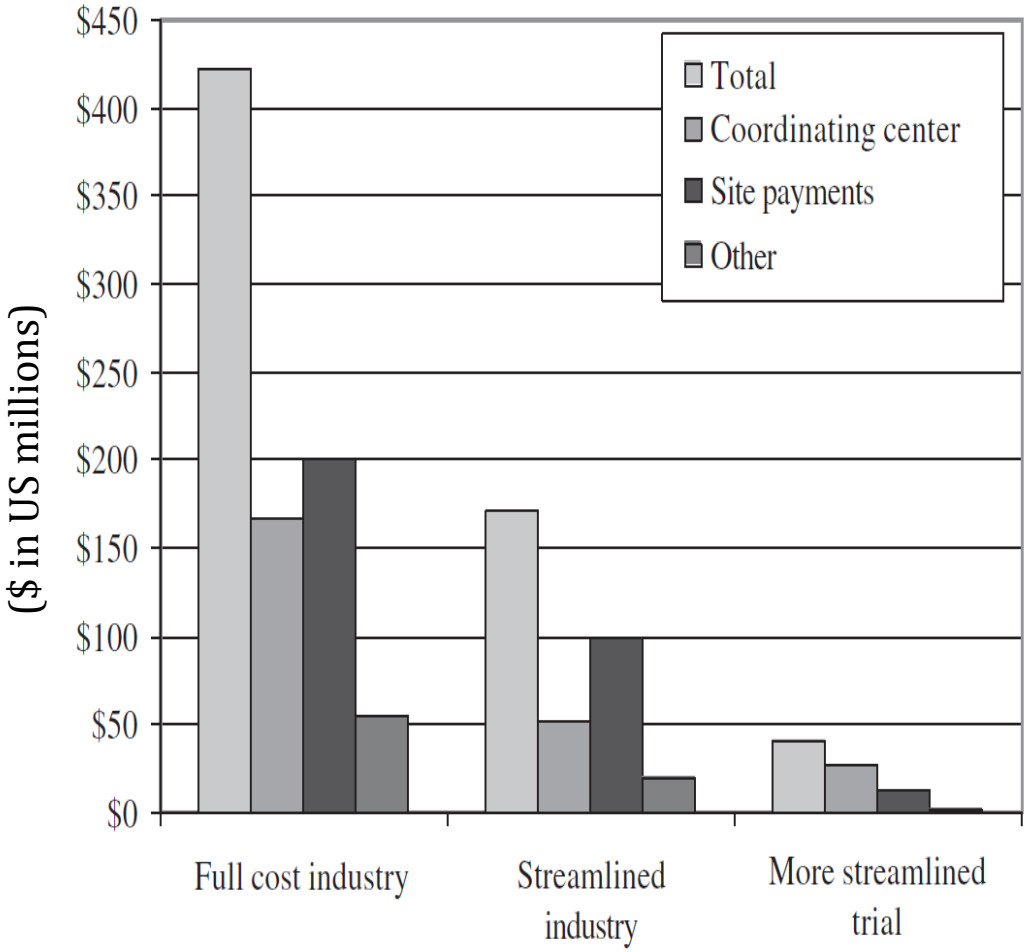
The Value of Large Simple Trials

- Can reliably detect most plausible small to moderate effects of particular treatments or exclude with statistical certainty the possibility of such effects
- Results of large simple trials
  - Are directly relevant to the wide range of patients seen in clinical practice
  - May be more rapidly incorporated into standard care of patients
- Design well-suited for post-marketing safety study
  - Minimizes the potential for bias yet is still relevant to real-world clinical practice

Cost of Large Complex Trials

- Large trials are sometimes seen as prohibitively expensive
- By some estimates, a streamlined approach to mega-trials could result in a cost reduction of more than 90%
- Thus, large simple trials can be conducted at very low cost per patient randomized

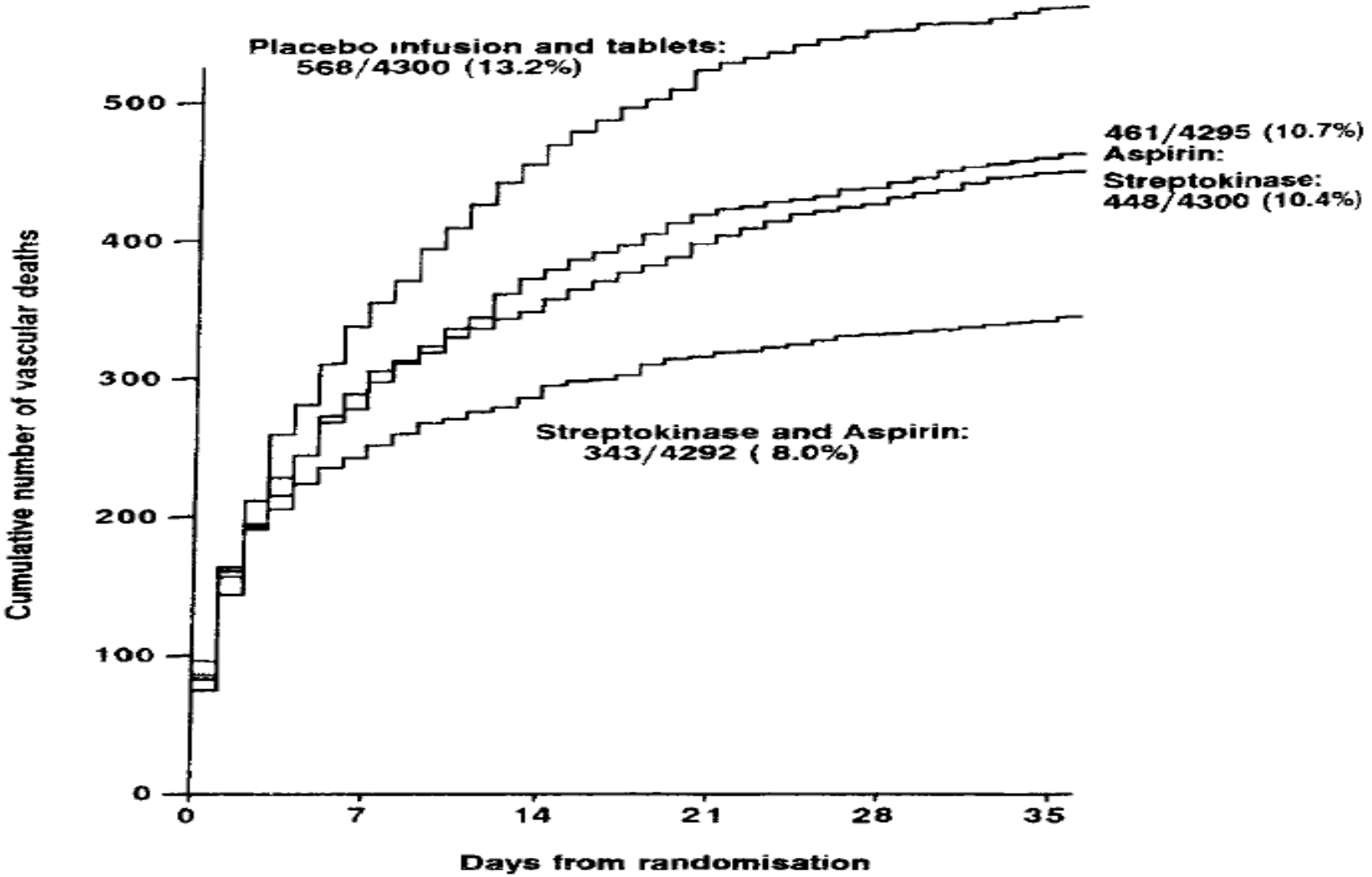


Eisenstein et al. Clin Trials 2008; 5: 75-84.

Real World Example: Second International Study of Infarct Survival (ISIS-2 trial)

- Randomized, placebo-controlled, 2 X 2 factorial design
  - Simple eligibility criteria – Patients within 24 hours of the onset of symptoms of suspected MI with no contraindications to streptokinase or aspirin
  - Patients were randomized to IV streptokinase, oral aspirin, both, or neither
- Study randomized 17, 187 patients with suspected acute myocardial infarction from 417 hospitals in 16 countries
- Physicians were free to use whatever additional treatment they considered necessary and compliance with allocated treatment was high

ISIS-2 Results



Lancet 1988 332: 349-360

ISIS-2 Results

Side-effect	Treatment allocation		Absolute *excess* with streptokinase (% SK– % Placebo)
	Streptokinase	Placebo infusion	
No randomised	8592	8595	
No with discharge form	8490	8491	
"Significant" hypotension and/or bradycardia	847 (10·0%)	173 (2·0%)	7·9%
Allergic reactions	374 (4·4%)	73 (0·9%)	3·5%
Any bleed	343 (4·0%)	99 (1·2%)	2·9%*
Gastrointestinal symptoms	100 (1·2%)	20 (0·2%)	0·9%
Arrhythmias	107 (1·3%)	28 (0·3%)	0·9%
Miscellaneous	99 (1·2%)	16 (0·2%)	1·0%
Patients with any of the above	1534 (18·1%)	383 (4·5%)	13·6%

*The bleeding caused by SK depended on whether the planned treatment involved iv heparin, sc heparin only, or no heparin (absolute excesses 5·3% SD 0·27, 2·6% SD 0·12, or 1·5% SD 0·14 respectively; $2p < 0·0001$ for trend).

Lancet 1988 332: 349-360

Public Health Impact of ISIS-2 trial

- ASA is now routine in the management of the acute MI patients
- Spurred additional work that further elucidated role of thrombolytics (also using LST designs!!)
- Because the finding was so robust and the outcome was so important, the impact on clinical practice was immediate and enormous
- It has been estimated that the change in practice (where now almost all patients presenting with AMI are treated with ASA) has saved tens of thousands of lives each year since these findings were published

FDA's Perspective

- FDA has increasing interest in clinical trial simplification
  - To decrease difficulty and cost of conducting trials
  - To encourage larger trials that are simple, pragmatic, and robust
  - To reduce unnecessary data collection (e.g., laboratory and/or safety data unlikely to result in a greater understanding of product), which is often cited as major reason physicians are unwilling to participate in clinical trials
- FDA emphasizes data quality, not quantity, and not proscriptive trial design

FDA's Efforts to Encourage the Use of Streamlined Trial Approaches

- August 24, 2011: Draft Guidance: Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring
  - Makes clear sponsors can use a variety of approaches to fulfill their monitoring responsibilities
  - Focuses monitoring activities on important and likely risks to critical data and processes
- February 2012: Draft Guidance: Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Post approval Clinical Investigations (AE Lite)
  - Helps clinical trial sponsors determine the amount and types of safety data that should be collected during late-stage premarket and post approval clinical investigations

Draft "AE Lite" Guidance

- Collection of data that are not useful and:
  - May be a disincentive to investigator participation in clinical trials
  - Deter conduct of large simple trials to obtain outcome data, data on long-term drug effects, and comparative effectiveness and safety data
- Selective, targeted safety data collection in late stages of development may:
  - Improve quality and utility of safety database and assessment without compromising integrity and validity of trial results and without loss of important information
  - Ease investigator burden
  - Lower costs, thereby encouraging conduct of large, simple trials

Final Thoughts

- Large simple trials designs are consistent with FDA's
  - Evolving overall approach to safety assessment which emphasizes a focus on information that is useful and informative rather than information that reflects what is already known
  - Risk-based monitoring approaches
  - Quality-by-Design and quality risk management initiative for clinical trials