Approaching Interim Analysis

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Advantages of Early Stopping

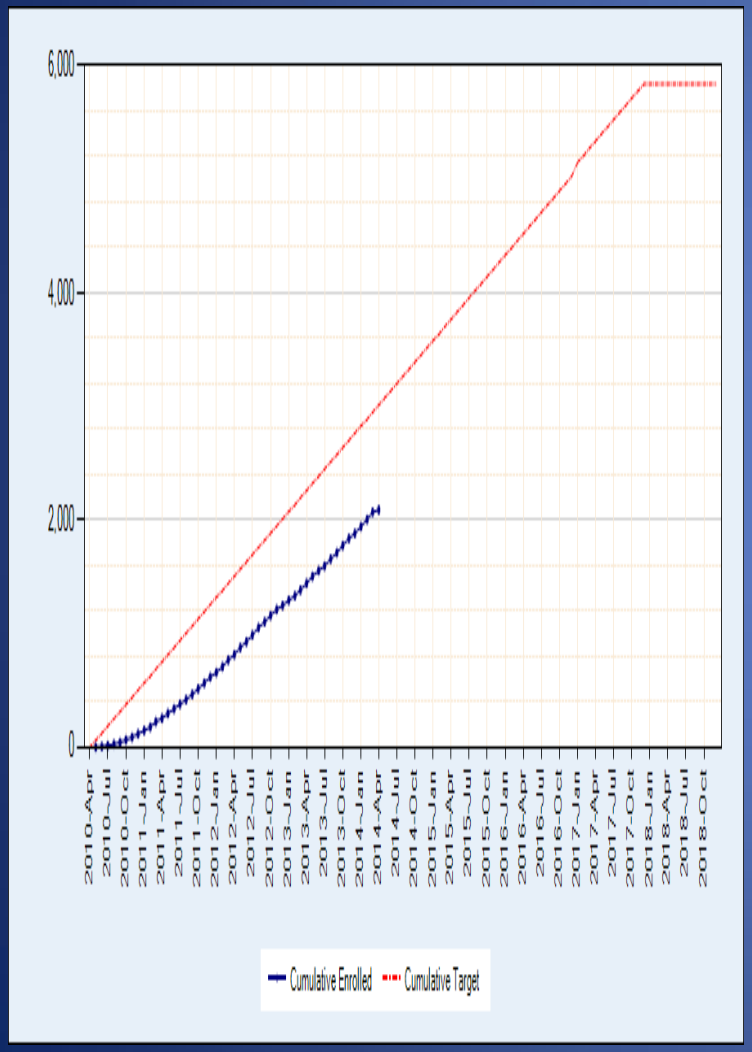
- Cost savings
  - ⇨ not wasting resources on duds if futile
  - ⇨ getting effective tx to market earlier
- Ethical issues
  - ⇨ not exposing subjects to inferior tx
  - ⇨ getting effective drug to patients earlier

Statistical Challenges of Interim Analysis

- High variability in early stages of the study with small N.
- If stop early for efficacy, tend to overestimate tx effect and its presicion[1].
- This bias may or may not affect meta-analysis that includes truncated RCTs[2-4].

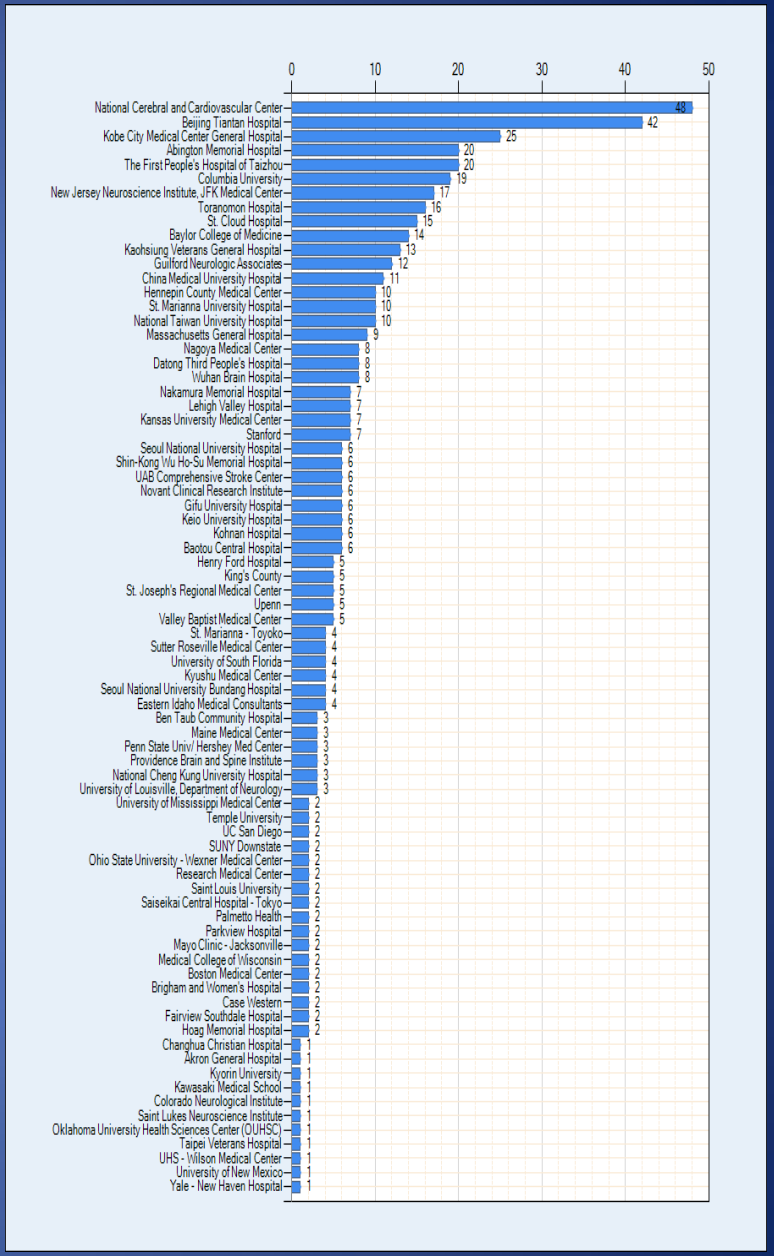
[1] Pocock S, White I. *Lancet* 1999;353:943-4.
[2] Bassler D, *et al. JAMA* 2010; 303: 1180-7; letters to the editors *JAMA* 2010;304:157-160.
[3] Bassler D, et al. SMMR 2011;
[4] Schou IM, Marschner IC. *SIM* 2013;32:4859-74.

Considerations for Interim Analysis



- Slow recruitment (hence, long study period)
- Multiple protocol amendments (unplanned AD)
  - ⇨ change in medical management (*e.g.*, new tx)
  - ⇨ change in patient characteristics
  - ⇨ affect cond'l power assumption?

- Large # of clinical sites
  - ⇨ variability in medical management
  - ⇨ learning curves amplified (with protocol, tx admin)
  - ⇨ may lead to dilution of tx effect
  - ⇨ treatment-by-site interaction could complicate the interpretation of IA results.



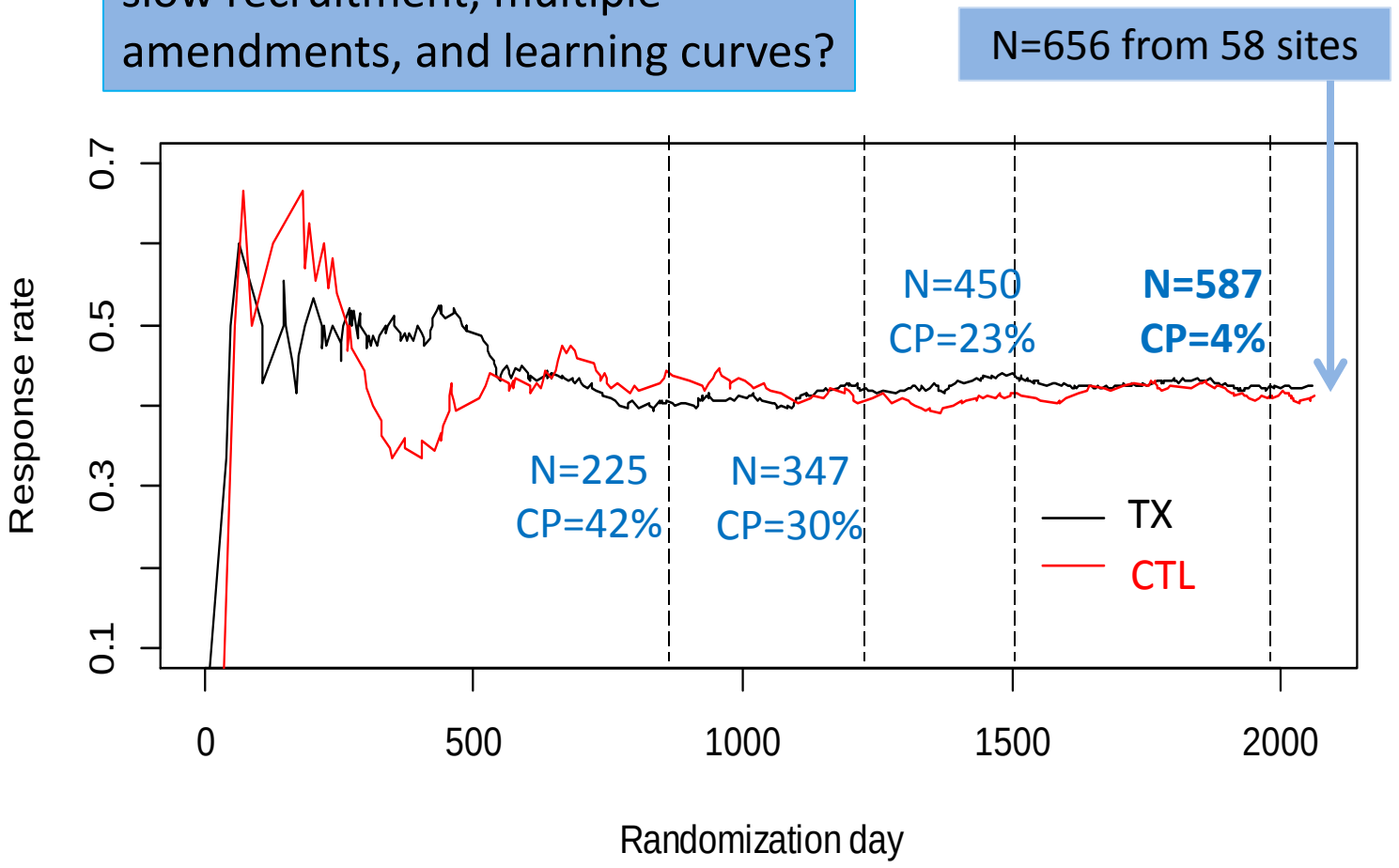
Example of IMS III Trial*

- Compare IV tPA (CTL) vs IV tPA + endovascular thromboysis (TX) in acute ischemic stroke patients.
- N=900; # sites ≈ 60.
- Had 4 protocol amendments with introduction of new devices with each.
- Very slow recruitment of subjects (~10/mo).
- 3 IAs planned with OF boundaries for efficacy.
- 3 conditional power analysis planned for futility.

* Broderick JP, et al. Stroke 2013;368:893-903; Yeatts SD, et al. Stroke 2014;45.

Example of IMS III Trial*

Was conditional power affected by slow recruitment, multiple amendments, and learning curves?



* Broderick JP, et al. Stroke 2013;368:893-903; Yeatts SD, et al. Stroke 2014;45.

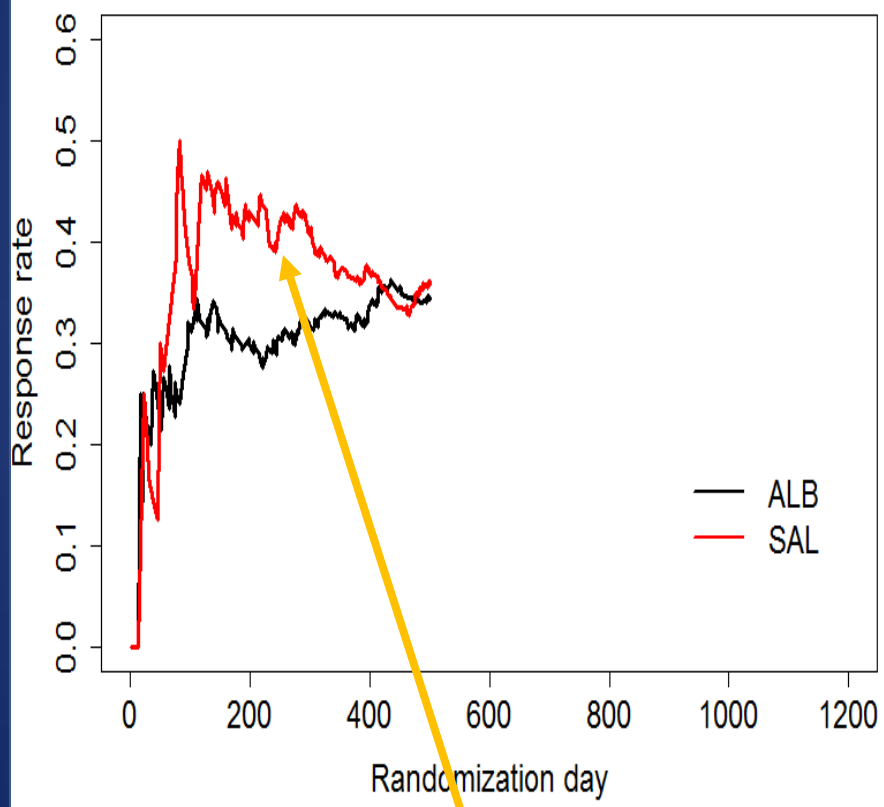
Example of ALIAS Parts 1* & 2** Trials

- Compare Saline (SAL) vs Albumin (ALB), above and beyond std of care (tPA or not), in acute ischemic stroke patients.
- N=1,800 in Part 1; N=1,100 in Part 2 with ~90 sites.
- Part 1 - stopped for safety concerns.
- Part 2 - 3 IAs planned with OF boundaries for both efficacy and futility.

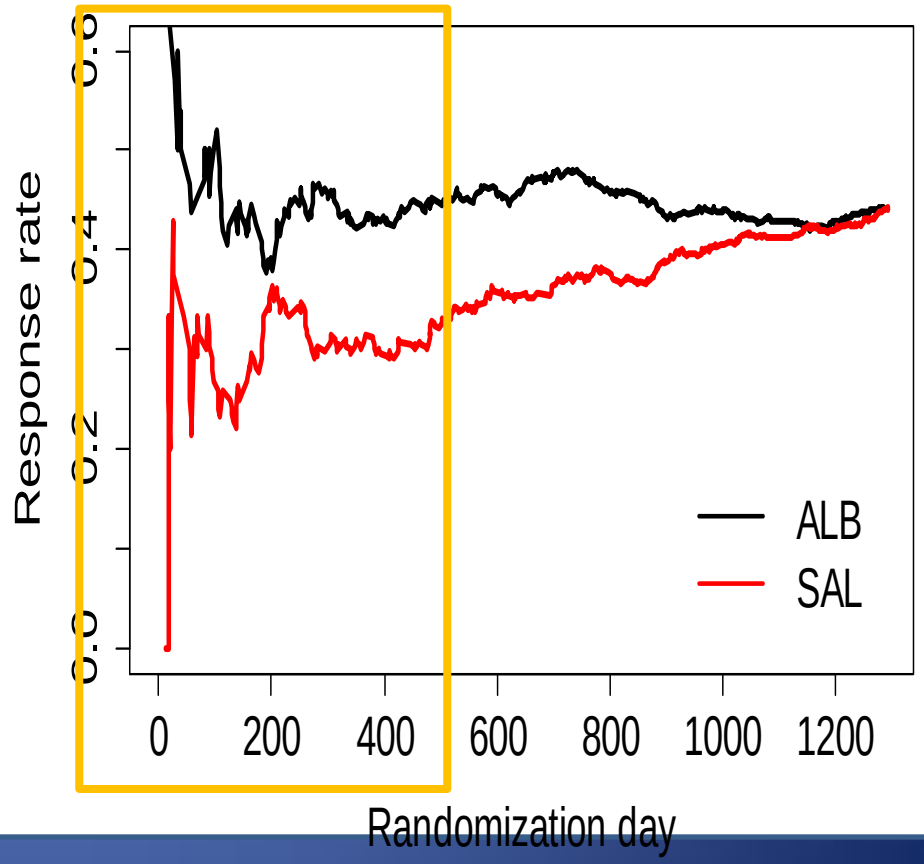
* Ginsberg MD, *et al. Stroke* 2011; 42(1):119-27; Hill MD, *et al. Stroke* 2011; 42(6):1621-1625
**Ginsberg MD, *et al. Lancet Neurol* 2013;12(11):1049-58

Example of ALIAS Parts 1* & 2** Trials

Like the Part 1 Trial, except in opposite direction



Part 2 (N=841; ~90 sites)



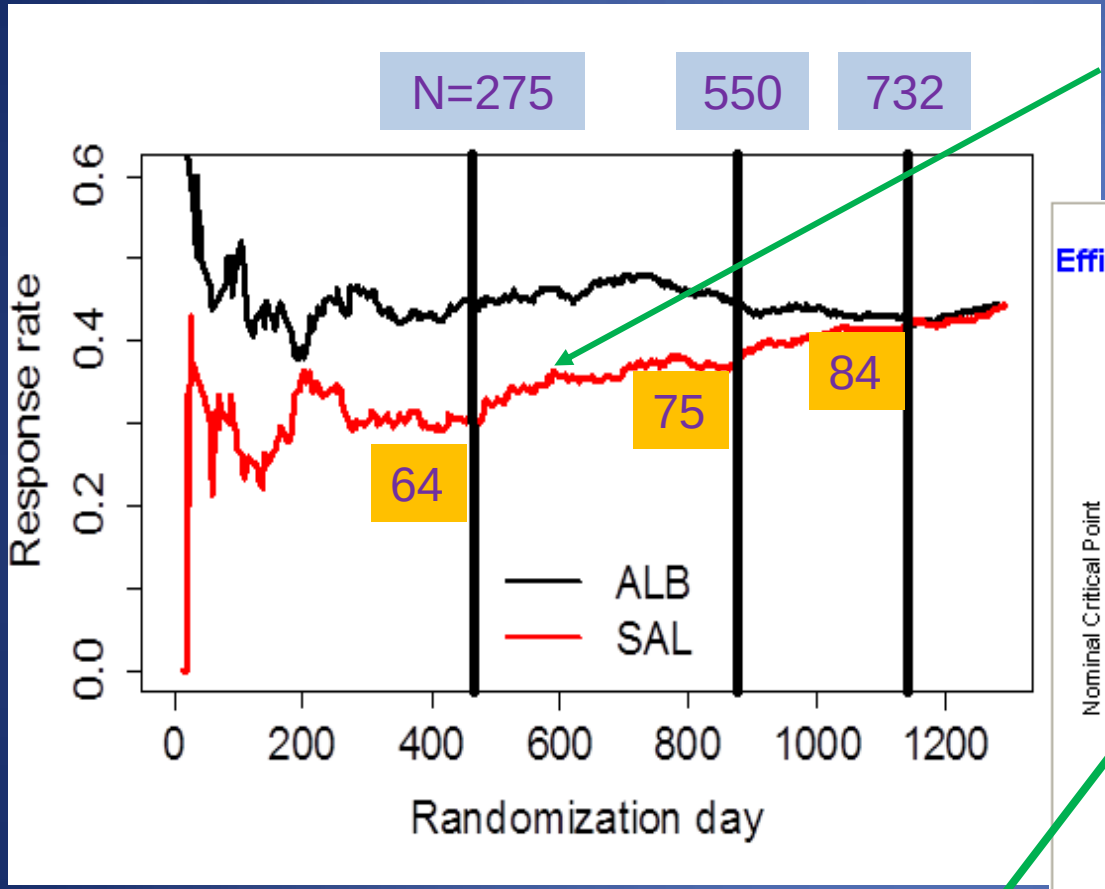
SAL similar to CTL in IMS III

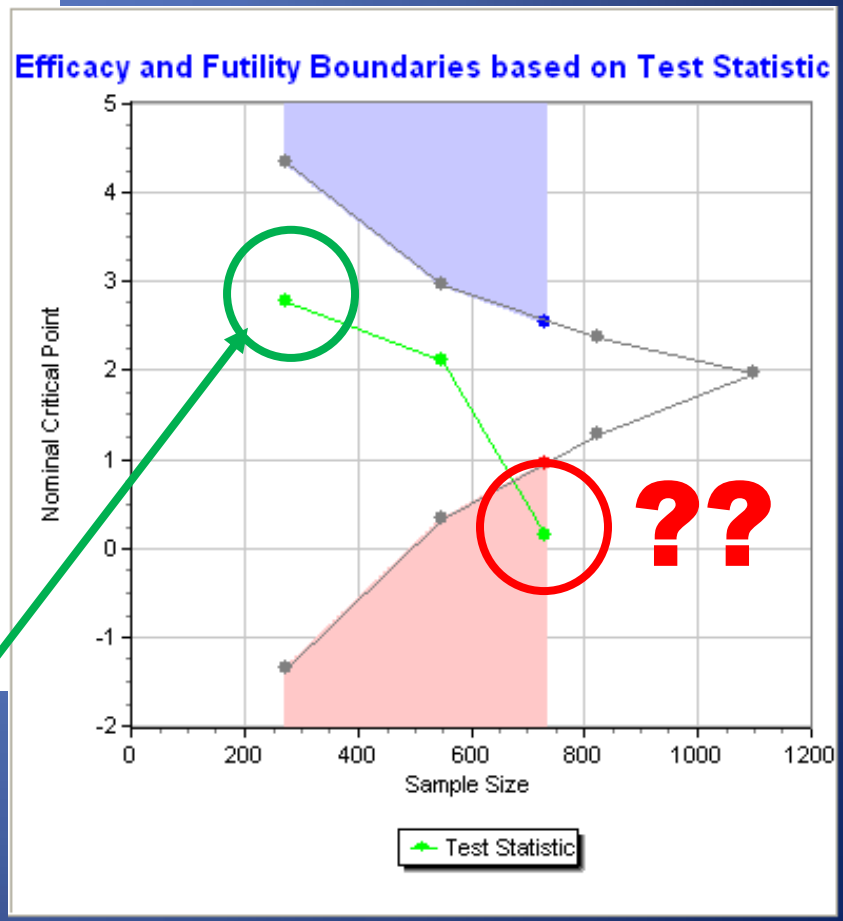
* Ginsberg MD, *et al. Stroke* 2011; 42(1):119-27; Hill MD, *et al. Stroke* 2011; 42(6):1621-1625

**Ginsberg MD, *et al. Lancet Neurol* 2013;12(11):1049-58

Example of ALIAS Part 2 Trial*

What, if anything, was happening in the SAL group over time?





Had we used PK boundary, we'd had stopped for efficacy

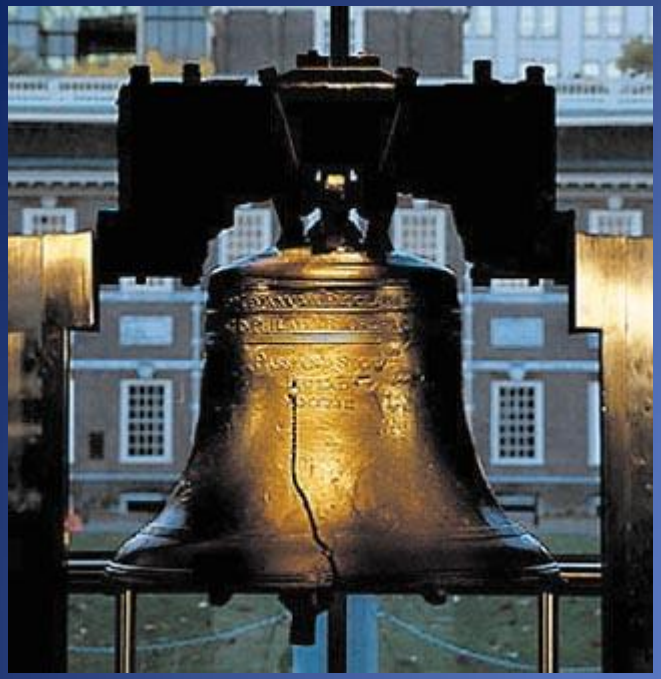
*Ginsberg MD, et al. *Lancet Neurol* 2013 Nov;12(11):1049-58

Summary

- Choose IA timing (esp. the first one) carefully – don't plan on one too early.
- Assess and address the learning curve, if any, of tx administration and protocol adherence.
- Be cognizant of temporal trends in patient characteristics, clinical standards of care, potential treatment-by-site interaction, etc.

(Simulation accounting for above factors at the design stage may be helpful.)

- Expect the unexpected.



Acknowledgement:

Lydia Foster, MS
Jamie Speiser, MS
Yanqiu Weng, DDS, PhD
ALIAS and IMS 3 Investigators

Funding from NINDS (U01-NS54630, U01-NS077306, U01-059041)

Thank You