Major Protocol Deviations:

Can we Help Investigator Site Staff to get it Right more Often?

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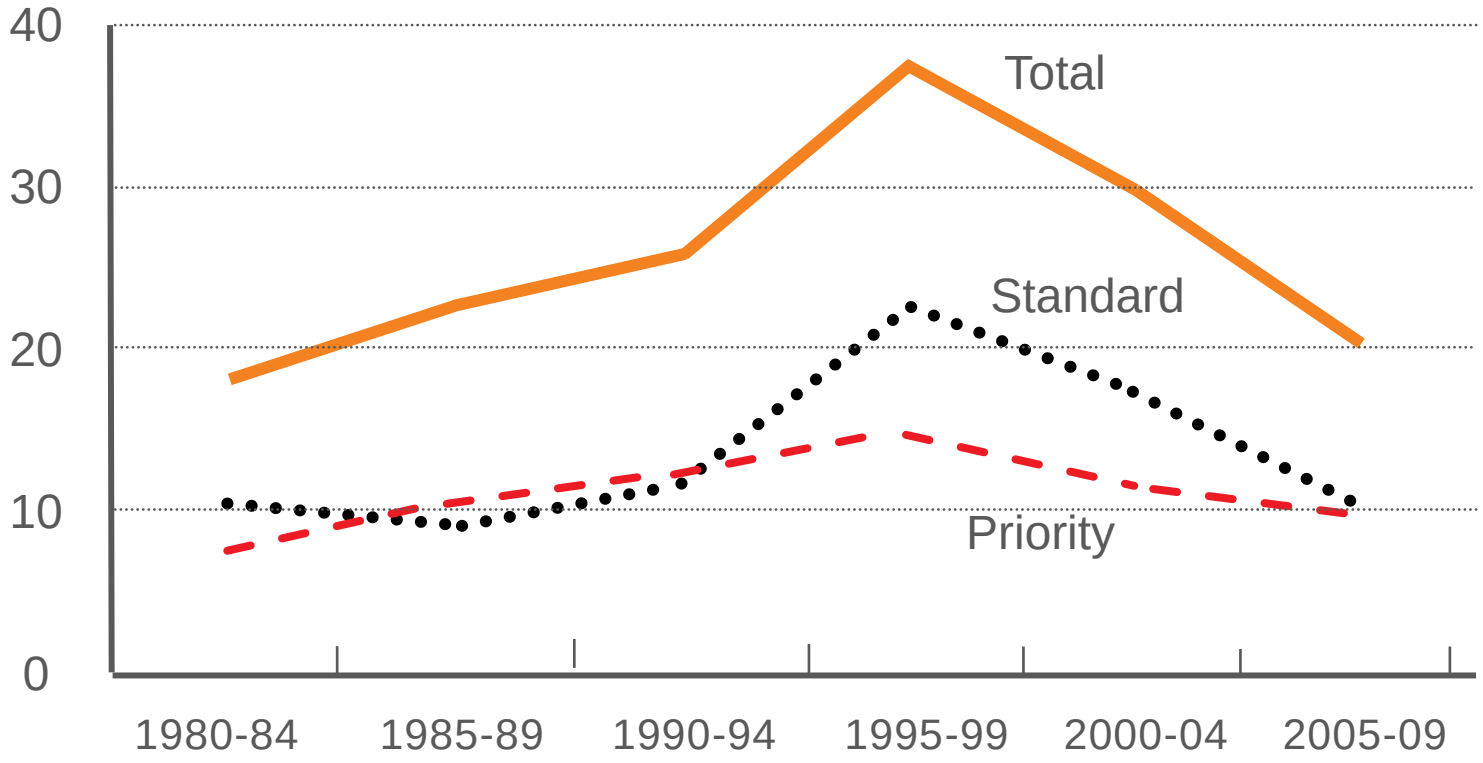
Average Annual Number of FDA Approvals



From: Kaitin KI DiMasi JA *(2011).* Clin Pharmacol & Therapeut **89** 183-188

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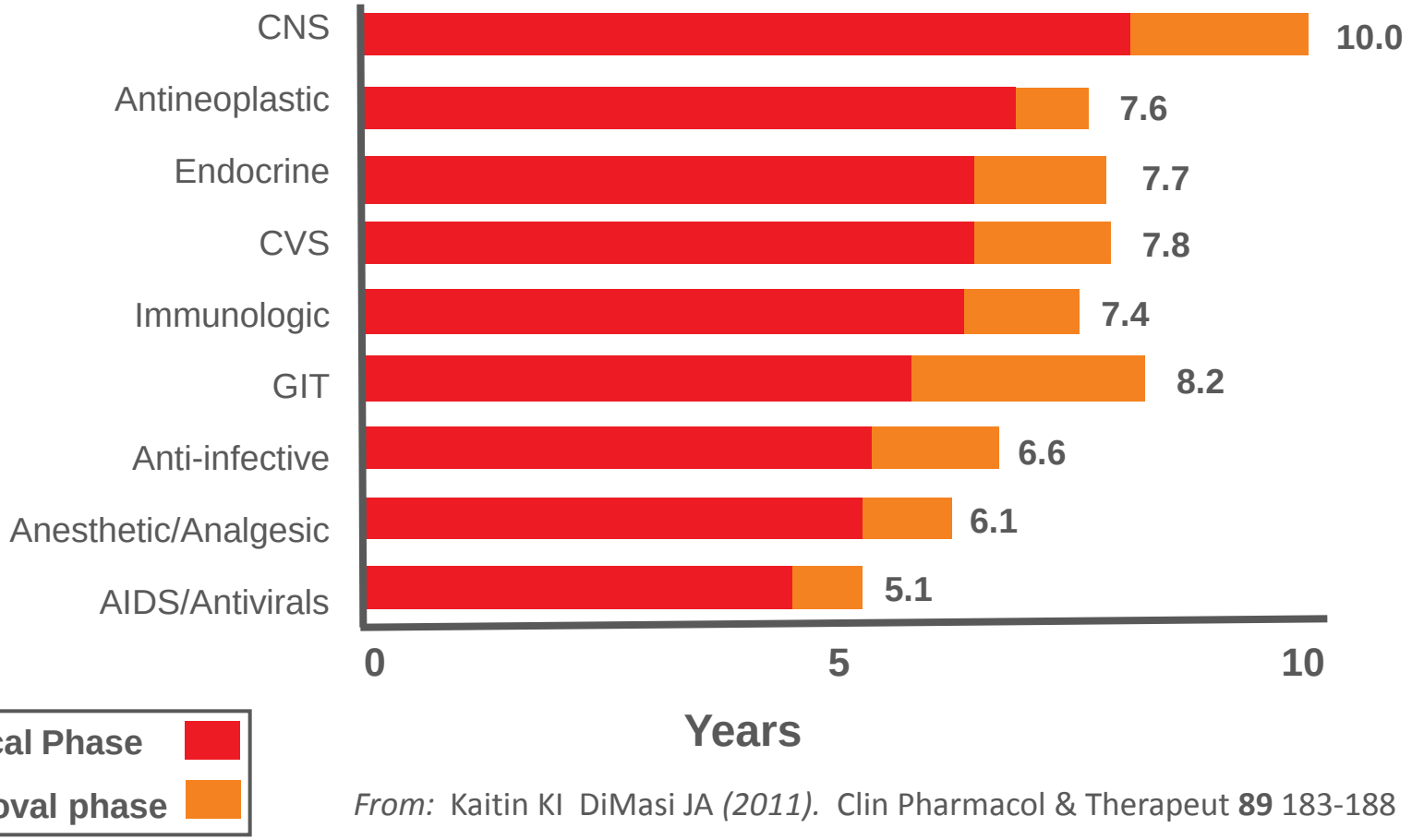
Mean Clinical and Approval Phase Times for FDA-Approved New Molecules and Biologics 2005-9



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Challenges in the Clinical Trial Pathway

- ***80% of clinical trials fail to finish on time.***
  - *Paraxel. Pharmaceutical R&D Statistical Sourcebook, 2001*
- ***Delays in attaining MA result in a cost to companies of as much as $1million a day in unrealised sales***
  - *Kermani F, Findlay G (2000). The Pharmaceutical R&D Compendium*
- ***Only 50% of successful Phase II trials meet their Phase III endpoints***
  - *Robert O'Neill, FDA, speaking at DIA EuroMeeting, Paris 2006*

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The Clinical Development Process

- ***A Cynical View?***
  - *First spend $ 200 million on discovering and carefully nurturing a new drug through non-clinical and first-in-man*
- ***Then, hand it over to a bunch of amateurs***
  - *Struggle to try to ensure it all works out!*

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Among the Problems are…

- *Ineffective training, remote in time from study startup*
- *Site staff, CRA and project team turnover during trial*
- *The traditional "Monitoring Model"*
- *Lack of Sponsor's insight into site performance until too late*
- *Poor decision support*
- *Increasingly complex protocols and procedures*
- *Proliferating 'tools' which site staff need to learn to use*

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The Increasing Burden on Study Sites

- ***From 1999-2005***
  - *The number of unique procedures and the frequency of procedures per protocol increased at the annual rate of 6.5% and 8.7%, respectively*
  - *Investigative site work burden to administer each protocol increased at an even faster rate of 10.5%*
  - *Study conduct performance (i.e., cycle time and patient recruitment and retention rates-worsened)*
  - *The number of protocol amendments, observed serious adverse events, and length of case report forms increased substantially*

*– Getz K, Wenger J, Campo RA et al. Am J Therapeut. (2008) **15**, 450-7*

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The Obvious Consequences of Poor Investigator Sites

- *Delayed recruitment*
- *Frequent non-compliances with protocol*
- *Expensive corrective action*
- *Delayed study close-out*
- *Delayed market approval*

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Power Calculations in Clinical Trials

Statistical considerations for a parallel trial where the outcome is a measurement

Request

[ ] Significance Level — [2] sided *(default is 0.05, two-sided)*

[ ] Standard Deviation of the outcome variable *(if known)*

Enter two of the following three values and the remaining value will be calculated

1. [ ] Total number of patients
2. [ ] Power (usually 0.8 or 0.9)
3. Minimal detectable difference (specify one of the following):
   a. [ ] Difference in means
   b. [ ] % Location of the mean of one treatement group in terms of a percentile of the other treatment group.

Calculate

Dr David Schoenfeld: *http://hedwig.mgh.harvard.edu/sample_size/js/js_parallel_quant.html*

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What's Missing from Power Calculations

- *Calculations assume uniform and complete investigator training*
- *Investigator-induced variance may render the calculation useless*

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Some Phase III Pitfalls in Oncology

- ***"Compassionate elasticity"***
  - *Stretching inclusion / exclusion criteria:*
  - *"The patient has no other hope than to get in this trial, so I'll gloss over some minor exclusions"*
- ***Consequence:***
  - *30-participant Phase II trial is 'contaminated' by 6 patients who shouldn't be in it (20% of participants)*
- ***Drug Fails Trial***

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Some Phase III Pitfalls in Oncology

- ***Misinterpretation of Adverse Events***
  - *Prostate cancer drug causes tumor lysis and release of PSA into plasma*
  - *Investigator site staffs' instinct is "Rising PSA is bad"*
  - *Patient is withdrawn / new medication is introduced / unblinding occurs*
  - *Rising PSA is reported as an AE*
  - *Trial is analysed by 'intention-to-treat'*
- ***Drug Fails Trial***

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Has EDC Helped?

- ***A Trial Visit in St. Chaos' Hospital***
  - *Log onto EDC site in office*
  - *Print out a paper copy of EDC screens*
  - *Go to other end of the Hospital*
  - *Conduct visit*
  - *Go to lunch*
  - *Come back to office to do some other work*
  - *Put visit record in basket on desk for later entry into EDC*
  - *Make mistakes in transcribing data*

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Average Time:Visit-to-Database Entry

- *Would 3 weeks surprise you as average for oncology trials?*
- *Given the narrow therapeutic margin, is that OK?*
- *Can we adequately identify risk, to protect participants?*

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The Most Serious Consequences of Poor Investigator Sites

- *Trial failure*
- *Trial failure*
- *Trial failure*

Up to 50% in Phase III!

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So, How does a Sponsor Know in Time what's Happening?

- *If monitors visit every 4-8 weeks?*
- *If time to database entry is average 3 weeks?*
- *When the data has then to be cleaned up of errors?*

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Modern Clinical Trial Quality Assurance?

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Criteria for Reporting Serious & Unexpected Suspected Adverse Reactions

- ***The IND sponsor must report such an event within 15 days if it was serious and within 7 days if it was fatal***
- ***A report could have important effects on patient monitoring and care***
- ***The sponsor must analyze in the aggregate events that are not interpretable as single cases and report them only if there is an observed imbalance between the drug-treatment group and a control group suggesting that the event is caused by the drug***
  - *FDA: Implementation March 2011*

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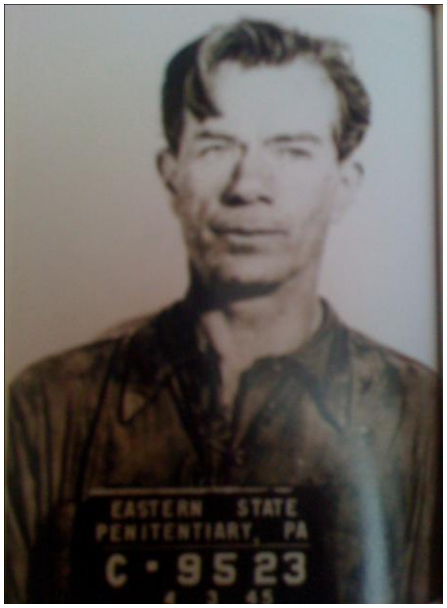
Where do we need to apply corrective action?

Investigator Sites



William "Willie" Sutton
(June 30, 1901 - November 2, 1980)

*"Go where the money is…
and go there often"*

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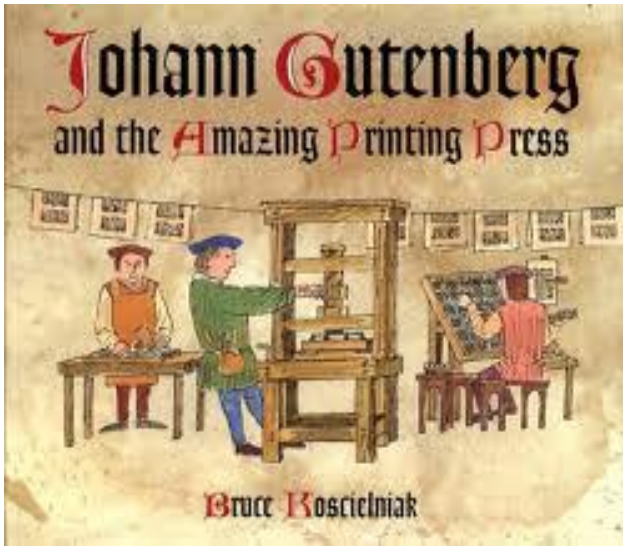
The Greatest Technological Advances in Clinical Trials



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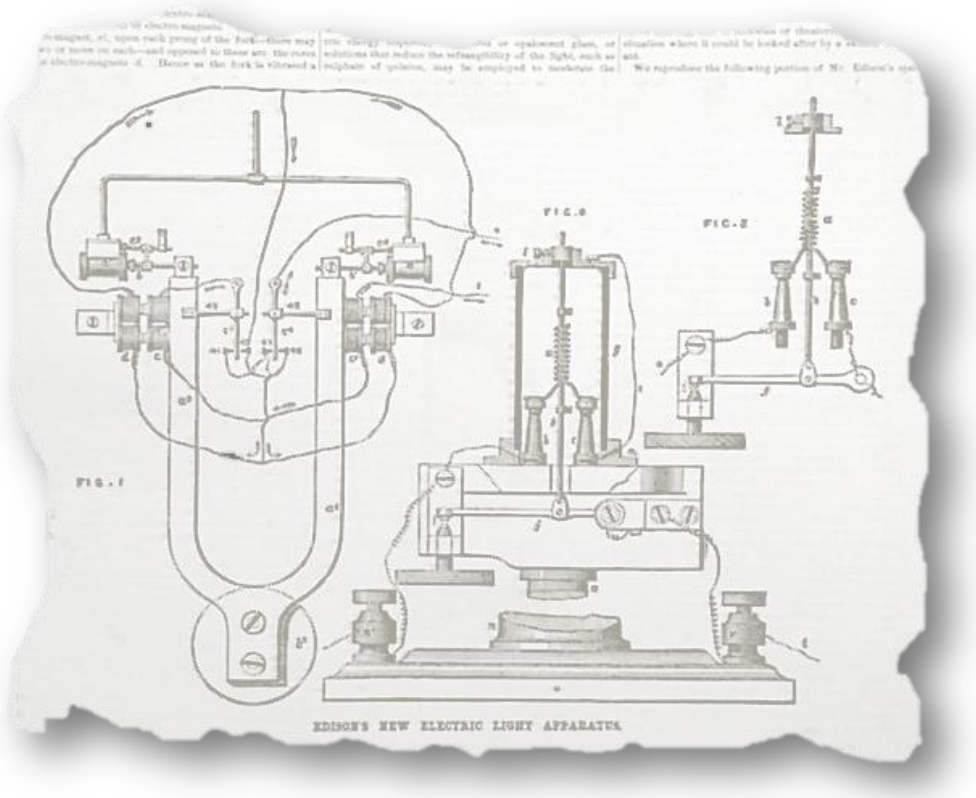
How can we help Investigator Sites?

Engineering Error Away



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How can we help Investigator Sites?

- ***We need ICT systems which:***
  - *Make investigator sites' lives much easier*
  - *Allow training that is effective, timely and available trial-long*
  - *Provide proper decision support to site staff*
  - *Engineer away error susceptibility*
  - *Deliver real-time data on site performance to Sponsors*
  - *Allow prompt entry of data into the database*

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Unless we truly help Investigator Sites…

- ***If we Persist with our present systems of trial conduct***
- ***Many drugs will fail that might have succeeded***
- ***Many patients will have their medical needs unmet***
- ***We will continue to waste huge resources through resistance to change***

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