

Major Protocol Deviations:

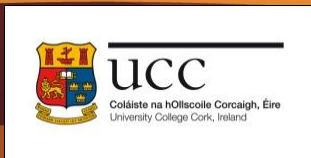
*Can we Help Investigator Site Staff
to get it Right more Often?*

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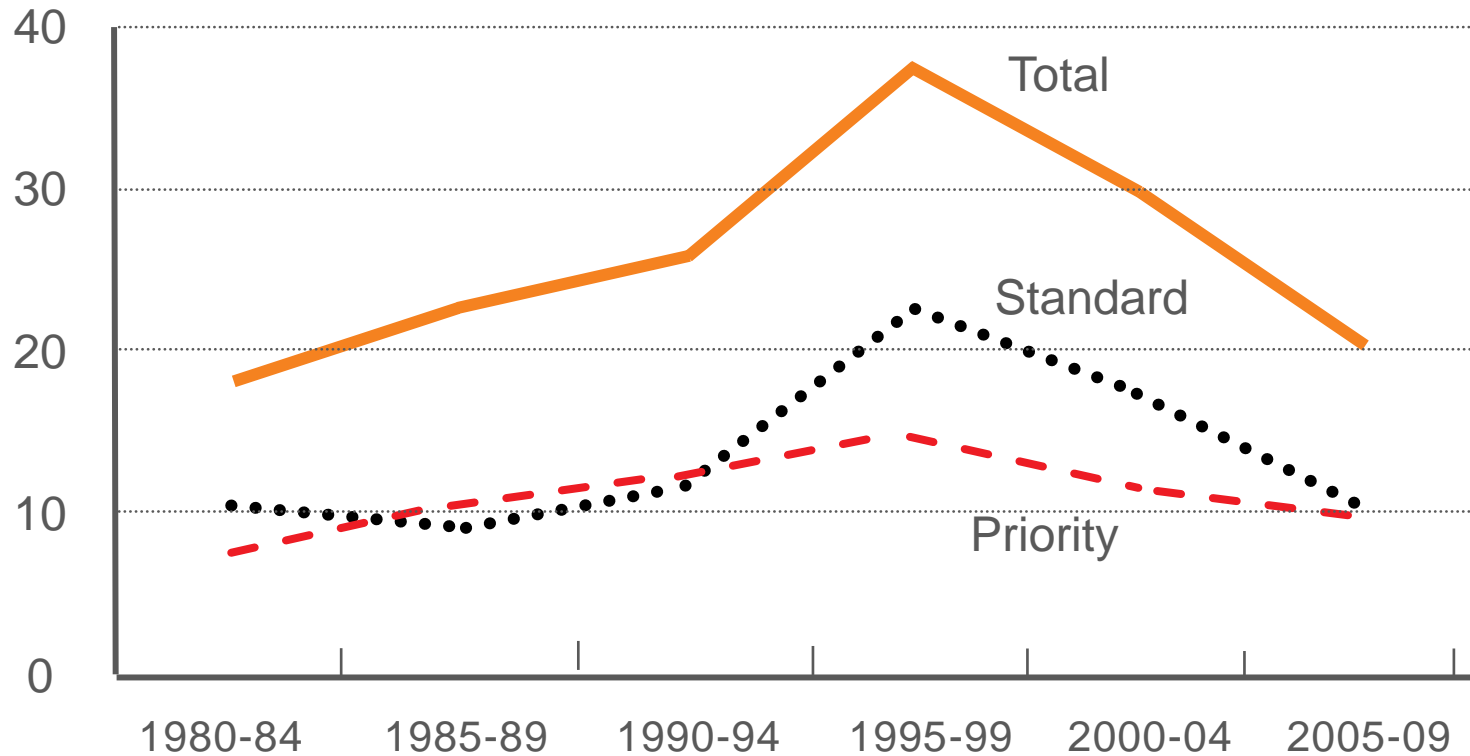
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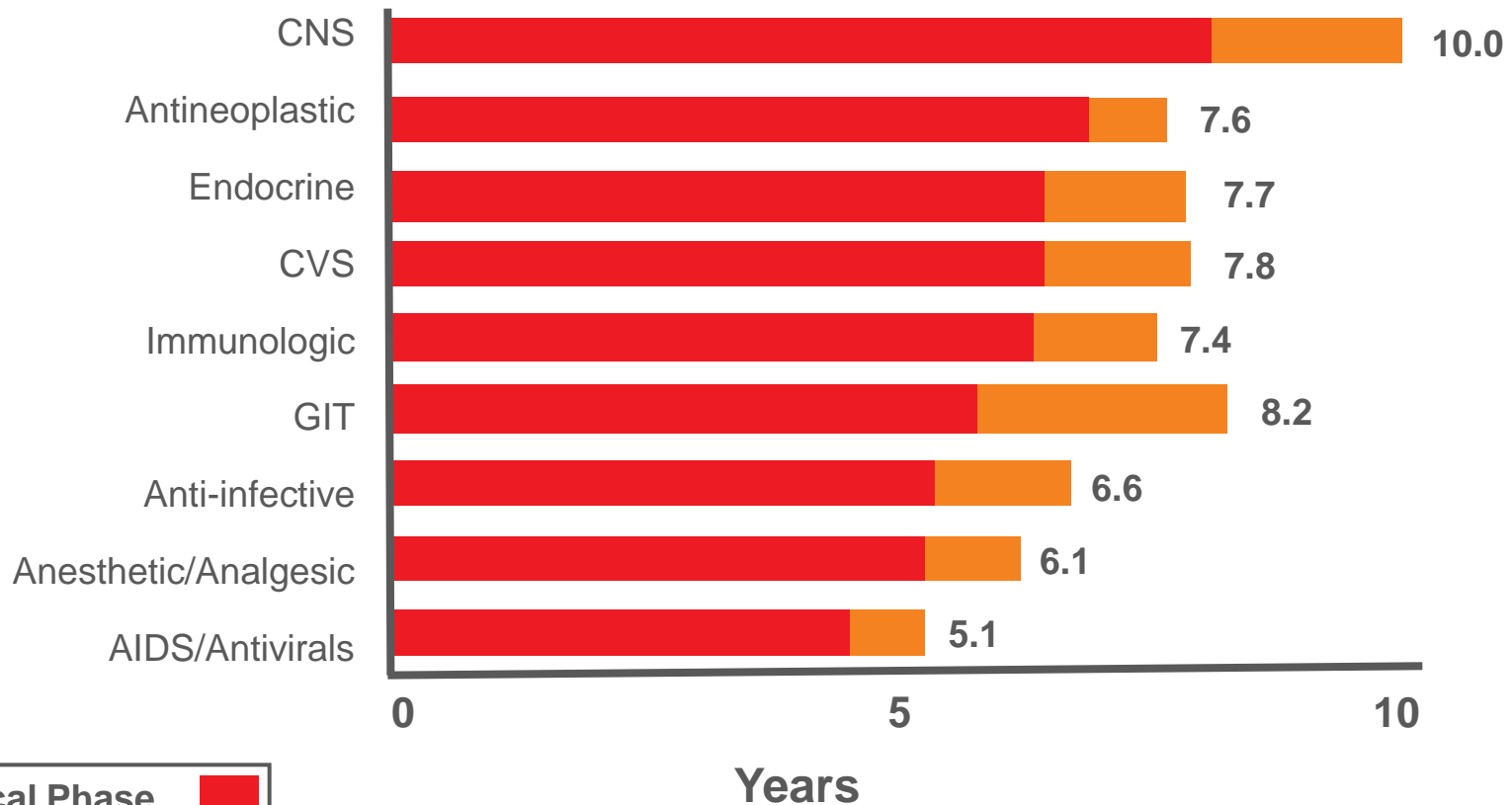


Average Annual Number of FDA Approvals



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

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



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

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*

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!*

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*

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*

The Obvious Consequences of Poor Investigator Sites

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

Power Calculations in Clinical Trials

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

Request

Significance Level — 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 treatment group in terms of a percentile of the other treatment group.

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

What's Missing from Power Calculations

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

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**

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**

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*

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?*

The Most Serious Consequences of Poor Investigator Sites

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

Up to 50% in Phase III!

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?*

Modern Clinical Trial Quality Assurance?

I'm calling to check
how many fires you've had
in the last eight weeks



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

Where do we need to apply corrective action?

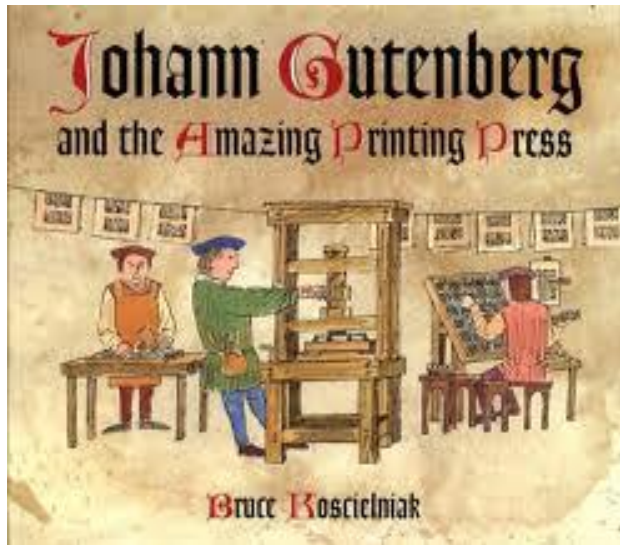
Investigator Sites



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

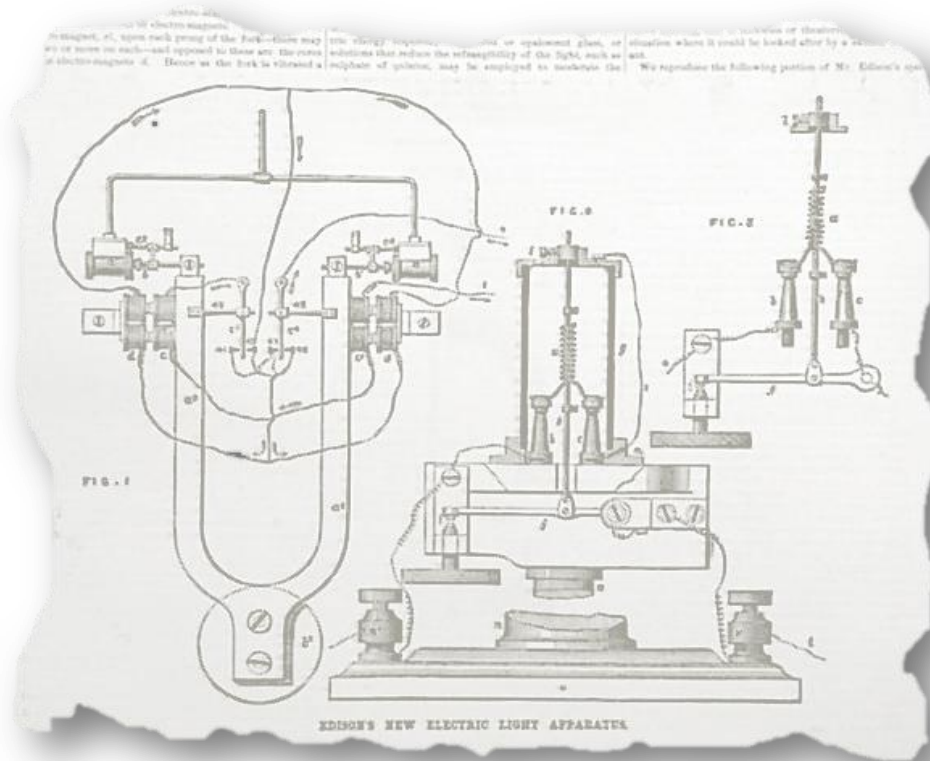
***“Go where the money is...
and go there often”***

The Greatest Technological Advances in Clinical Trials



How can we help Investigator Sites?

Engineering Error Away



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*

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*