The Usage, Perception and Considerations of Adaptive Designs. A Short Term Fad or a Long Term Goal?

CCRA Seminar, 14th July 2014

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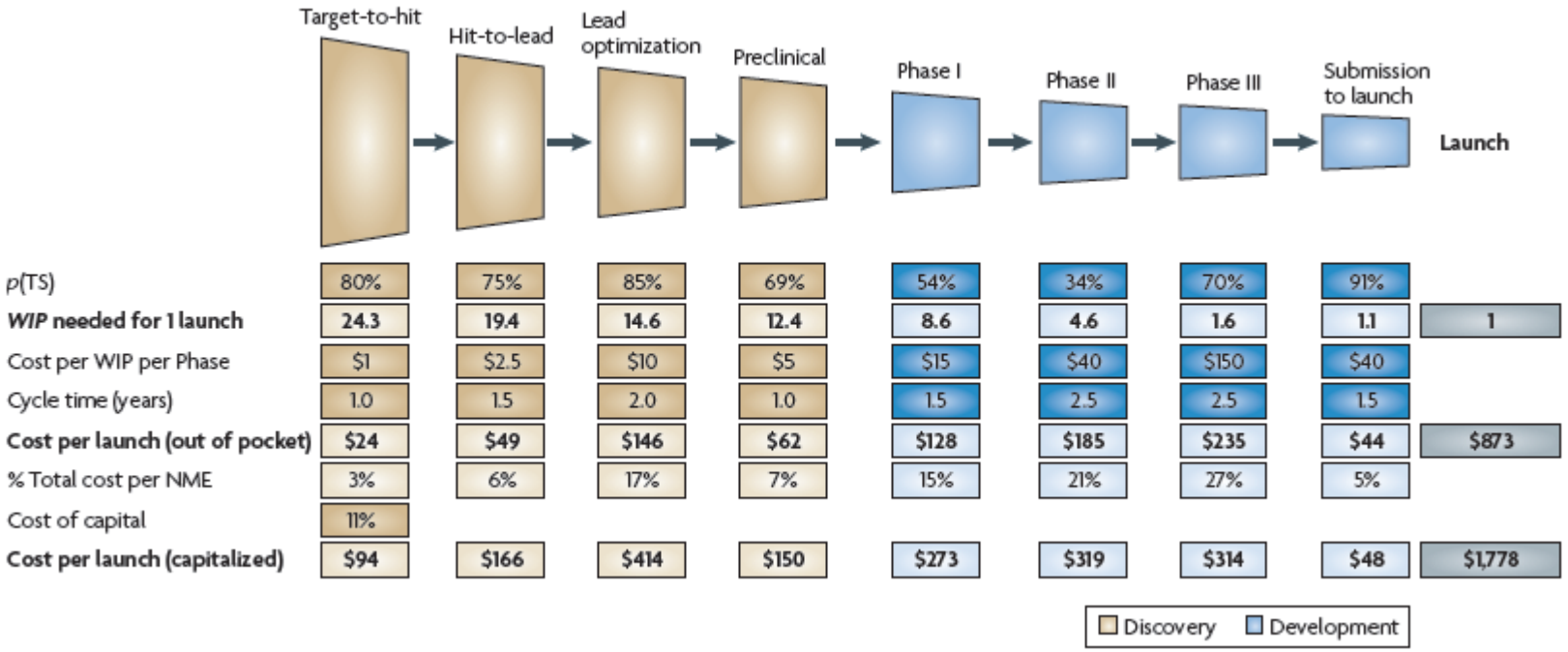
Why adaptive designs? – Some Statistics

- Low probability of success for novel candidate at Phase I (FDA Critical Path, 2004)
  - 8% chance of reaching market
- High failure rate (Kolis & Landis, 2004)
  - 40% phase II
  - 45% phase III
- Developing cost escalating (FDA Critical Path, 2004)
  - Costs of bringing new drug to market ($8 Million to $1.7 Billion)
- 90% of drugs fail

The Cost of Drug Development
Eli Lilly R&D Productivity Model



p(TS)	80%	75%	85%	69%	54%	34%	70%	91%	
***WIP* needed for 1 launch**	24.3	19.4	14.6	12.4	8.6	4.6	1.6	1.1	1
Cost per WIP per Phase	$1	$2.5	$10	$5	$15	$40	$150	$40	
Cycle time (years)	1.0	1.5	2.0	1.0	1.5	2.5	2.5	1.5	
Cost per launch (out of pocket)	$24	$49	$146	$62	$128	$185	$235	$44	$873
% Total cost per NME	3%	6%	17%	7%	15%	21%	27%	5%	
Cost of capital	11%								
Cost per launch (capitalized)	$94	$166	$414	$150	$273	$319	$314	$48	$1,778

Discovery Development

Paul et al Nat Rev Drug Disc. 2010;9:203-214

Lack of efficacy remains the main reason for development failure

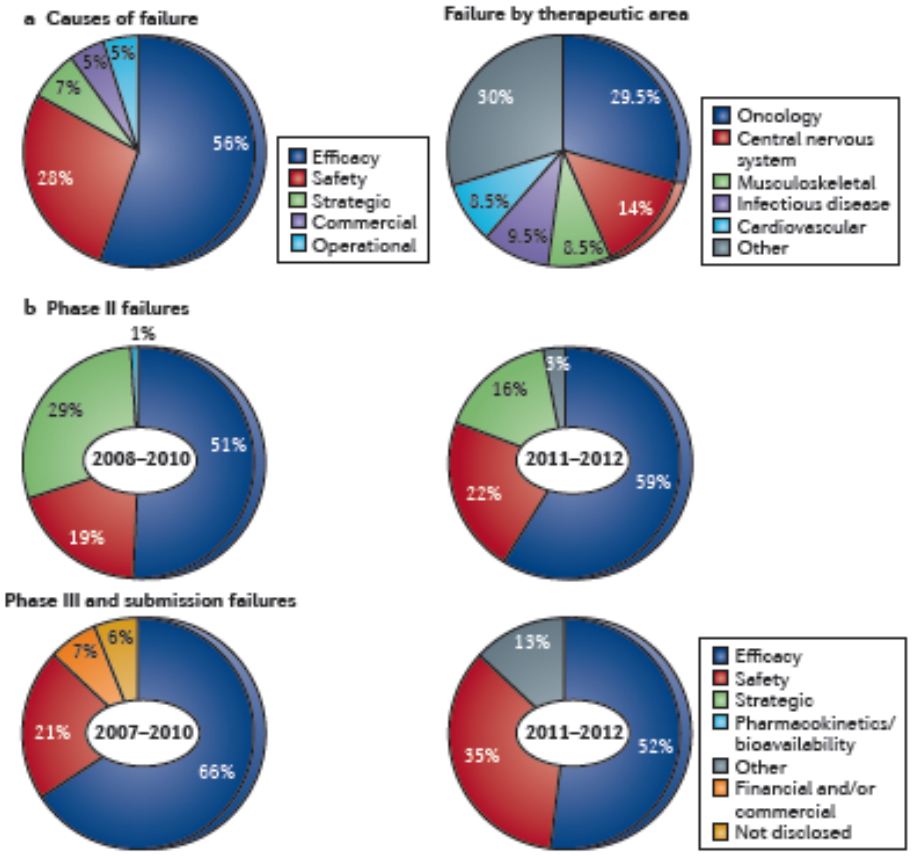


Figure 1 | **Trends in attrition rates.** **a** | Of the 148 failures between Phase II and submission in 2011 and 2012, reasons were reported for 105; the majority of failures were due to lack of efficacy, as shown on the left. On the right, the 105 reported failures are broken down according to therapeutic area. **b** | Comparison of the reasons for failures in Phase II and Phase III trials in 2011 and 2012 with those in earlier periods that we reported previously (see main text for details). Data are from Thomson Reuters, *Drugs of Today* © Prous Science S.A.

Arrowsmith & Miller, Nature Rev Drug Disc 2013;12:569

Definition

- **Adaptive design**
  - A multi-stage study design that uses accumulating data to decide on how to modify aspects of the study without undermining the validity and integrity of the trial.
  - Should be adaptive by “design”, not remedy for poor planning
  - Numerous types of adaptive designs

Adaptive Ideas Are Not New (Thompson, Biometrika, 1933)

ON THE LIKELIHOOD THAT ONE UNKNOWN PROBABILITY EXCEEDS ANOTHER IN VIEW OF THE EVIDENCE OF TWO SAMPLES.

By WILLIAM R. THOMPSON. From the Department of Pathology, Yale University.

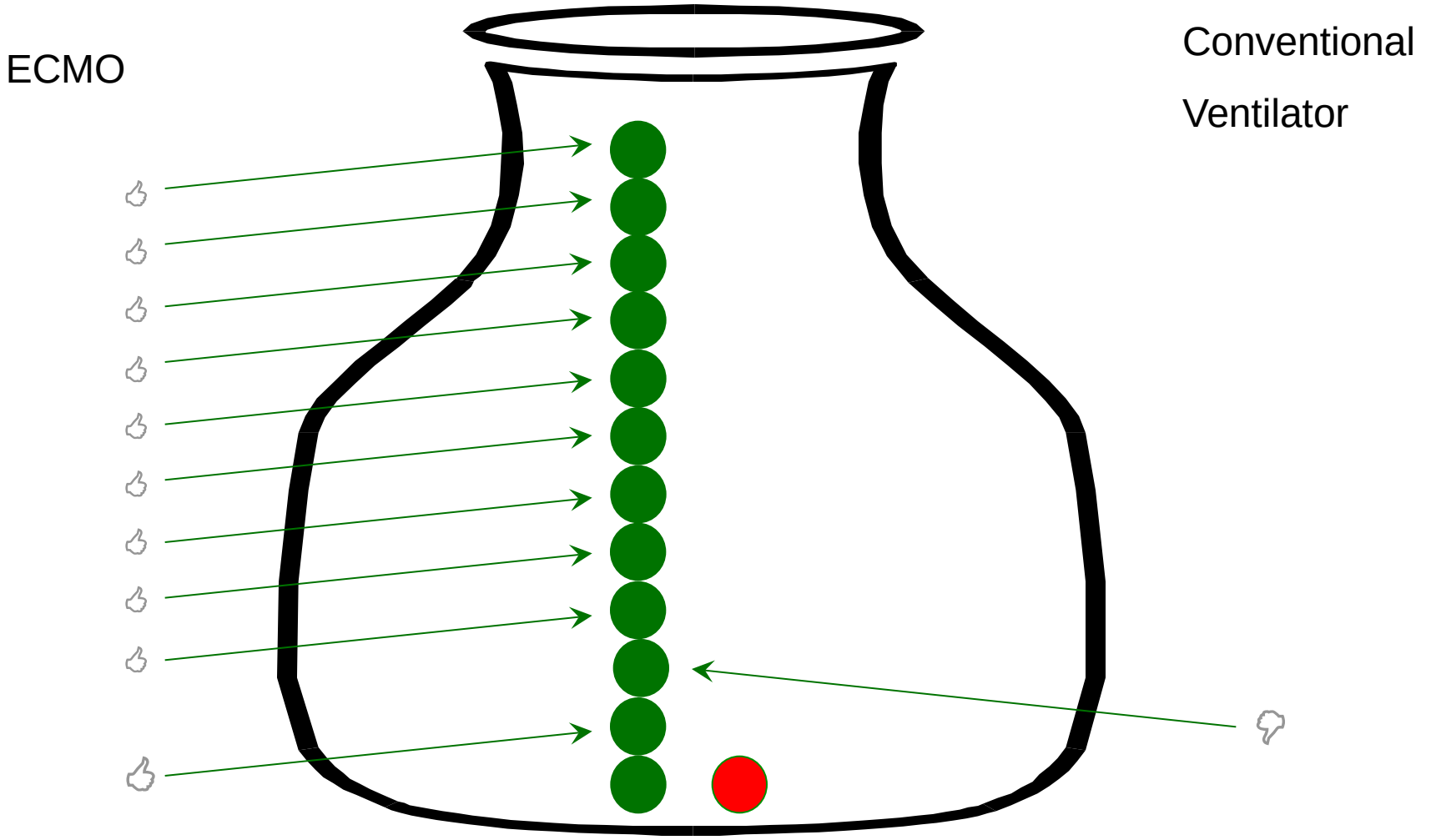
Thus, if, in this sense, P is the probability estimate that one *treatment* of a certain class of individuals is *better* than a second, as judged by data at present available, then we might take some monotone increasing function of P, say $f_{(P)}$, to fix the fraction of such individuals to be treated in the *first manner*, until more evidence may be utilised, where $0 \leqslant f_{(P)} \leqslant 1$; the remaining fraction of such individuals $(1 - f_{(P)})$ to be treated in the *second manner*; or we may establish a probability of treatment by the two methods of $f_{(P)}$ and $1 - f_{(P)}$, respectively. If

- Ethical Design – concentrating on delivering the best treatment to the most patients
- Forerunner of the Randomised Play the Winner Design

What Put Adaptive Designs Back?

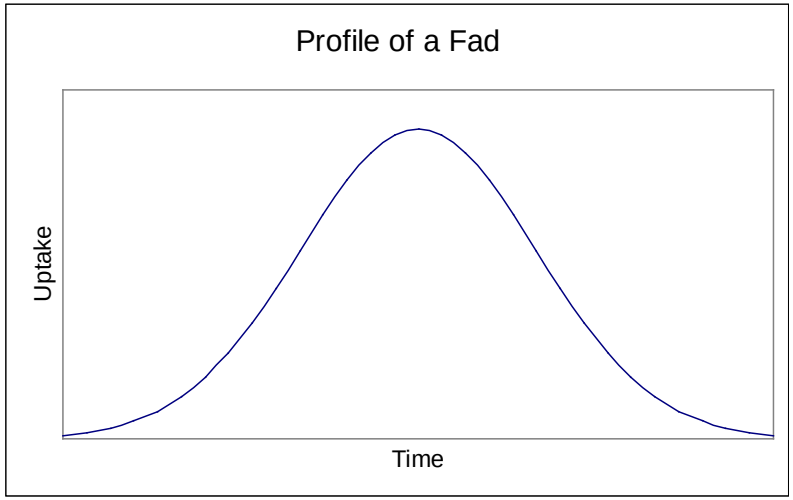
- Study in Extra Corporeal Membrane Oxygenation (ECMO)
  - Published by Bartlett et al (1985)
  - New-born infants with severe respiratory failure – Mortality
  - Extra Corporeal Membrane Oxygenation vs Traditional Ventilator
  - Phase I trials >50% survival on ECMO
  - Optimal Therapy : survival < 20 %
  - Chose Randomised Play-the-Winner (RPW) design

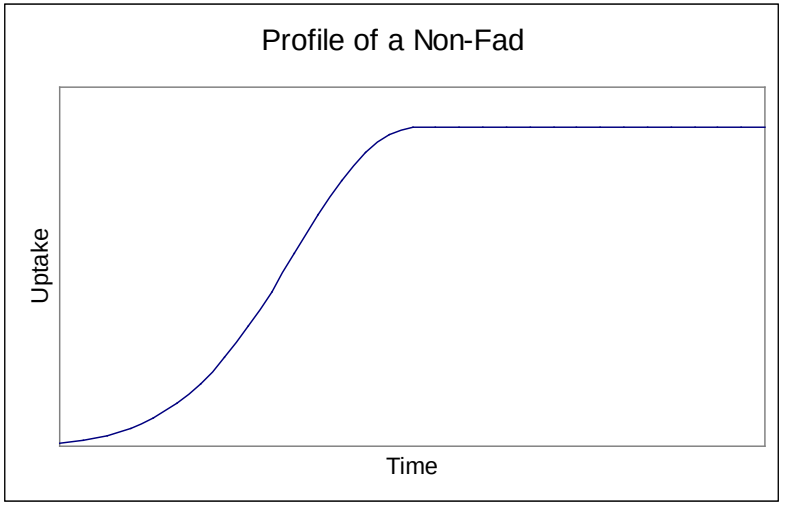
Randomised Play-the-Winner -Urn Model (ECMO)



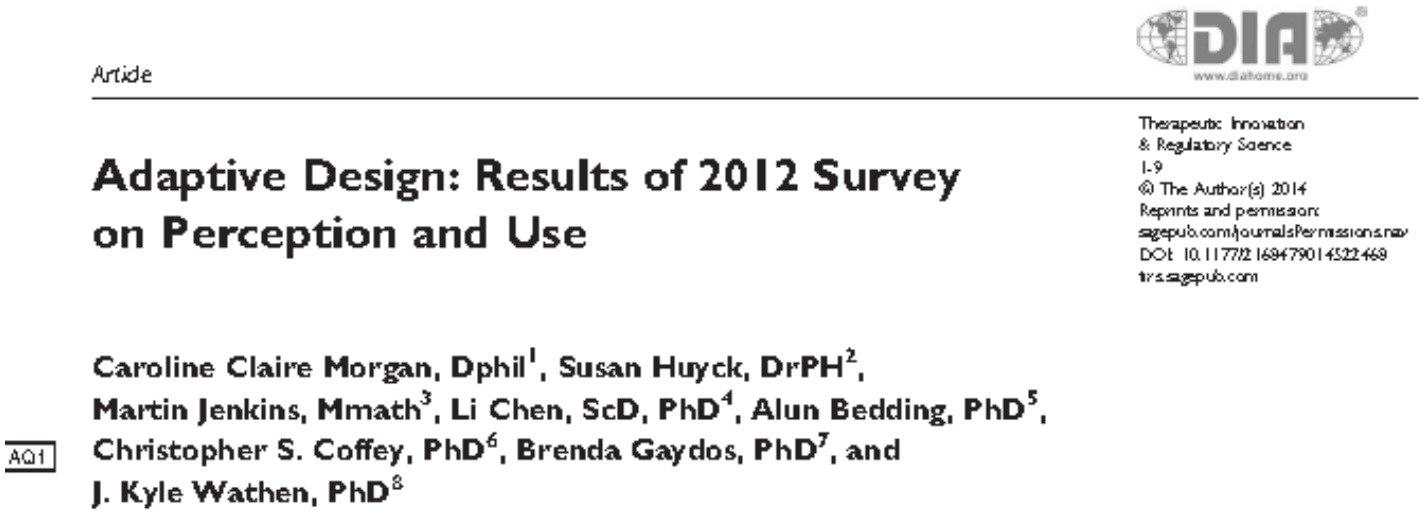
Are they a Fad?

- Flexible and Adaptive Designs: A Fad or the Future of Clinical Research?
  - This year's most popular Christmas Toy may be a fad
  - Late 1950's – the hula-hoop was a fad
  - At the moment it is loom bands
  - Smartphones are not a fad





DIA Adaptive Design Scientific Working Group (ADSWG)
Survey Subteam



Article

Adaptive Design: Results of 2012 Survey on Perception and Use

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AQ1

Drug Information Journal (In print)

ADSWG Survey Subteam Objective

To gather information on the **perception** and **use** of **adaptive designs** for clinical development programs in the industry and academia, in order to identify any **persistent barriers** to implementing such designs and **provide recommendations** to overcome these challenges

ADSWG 2012 Survey Timelines

- Q4 2011 – Initiated Questionnaire & Literature/Registry Reviews
- Q1/Q2 2012 – Presentation of Preliminary Results
  - DIA Annual Euromeeting, Copenhagen
  - DIA Annual China meeting, Shanghai
  - SCT Annual Meeting, Miami
- Q4 2012 – Complete Questionnaire & Literature/Registry Reviews
- Q4 2012 – Questionnaire Specific to Academia
- Q1 2013 – Publication to be Submitted to DIA Journal

ADSWG 2012 Survey

- Questionnaire:
  - 10 Adaptive Design (AD) related questions asked to pharma/biotech/academia/NGOs/CROs
- Literature and registry reviews:
  - Standard list of search items used to identify possible Ads
  - Selection of questions asked (similar to those in the questionnaire)
- Literature review: 7 scientific journals reviewed for ADs from Jan 2000 to Sep 2011
- Registry review: AD trials starting between Jan 1996 and Sep 2011 and published on ClinicalTrials.gov

Questionnaire: Methods

- Questionnaire distributed in October 2011
  - via email to 92 organisations worldwide: pharma/biotech/academia/NGOs/CROs
  - via the October PSI eBulletin

- 18 participants:
  - 11 pharma/biotechs
  - 1 academic institution
  - 6 CROs who propose adaptive trial design services

- Compared to results from 2008 Survey (PhRMA ADWG)
  - 13 medium to large pharma companies + 3 CROs
  - Case studies of ADs designed/conducted from January 2003 to March 2008

Questionnaire: Key Limitations

- Questionnaire
  - Not fully representative
    - Few biotech and academic participants
    - No responses from device companies
    - Difficult for large pharma companies to obtain exhaustive list of ADs considered/implemented worldwide
  - Confidentiality impact, especially with regard to disease areas and submission status
  - Difficult to compare to results of 2008 AD survey
    - Case studies in 2008 *vs* summaries per organization in 2012
    - Only identification of barriers to use of ADs was directly comparable

Questionnaire: Participants

Abbott
Amgen
Aptiv Solutions
AstraZeneca
Cardinal Systems
Cytel
Eli Lilly
George Institute
GSK
Geron
Icon
Iowa University
Quintiles
J&J
Merck
Novartis
Pfizer
Sanofi-aventis

Questionnaire: AD Categories

- Adaptive designs were split into two categories for the purposes of the questionnaire:
  - GSDs / blinded SSR
    - Standard group sequential designs (with early stopping for efficacy/futility) and/or blinded sample size re-estimation, with no other adaptation;
  - Other ADs
    - All other AD with at least one adaptation other than or in addition to early stopping for efficacy/futility and/or blinded SSR (for example, unblinded sample size re-estimation).

Questionnaire: Exploratory/Confirmatory

ADs designed between 1st January 2008 and 1st September 2011

- GSDs/blinded SSR:
  283 studies

- Other ADs:
  153 studies

Other ADs

2012 Survey

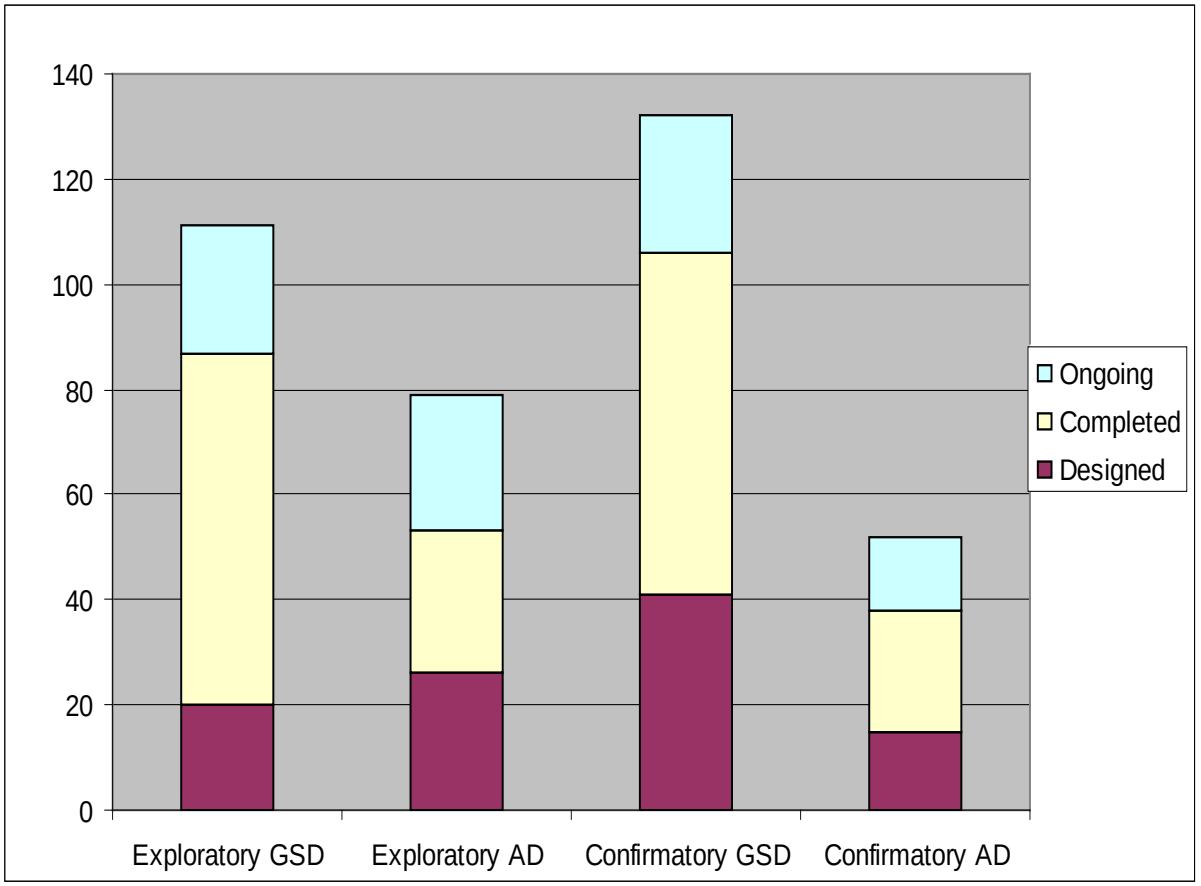
100/153 exploratory

53/153 confirmatory

2008 Survey

30/59 exploratory

29/59 confirmatory



Note: One organisation did not answer this question and one did not split ADs by designed/ongoing/completed

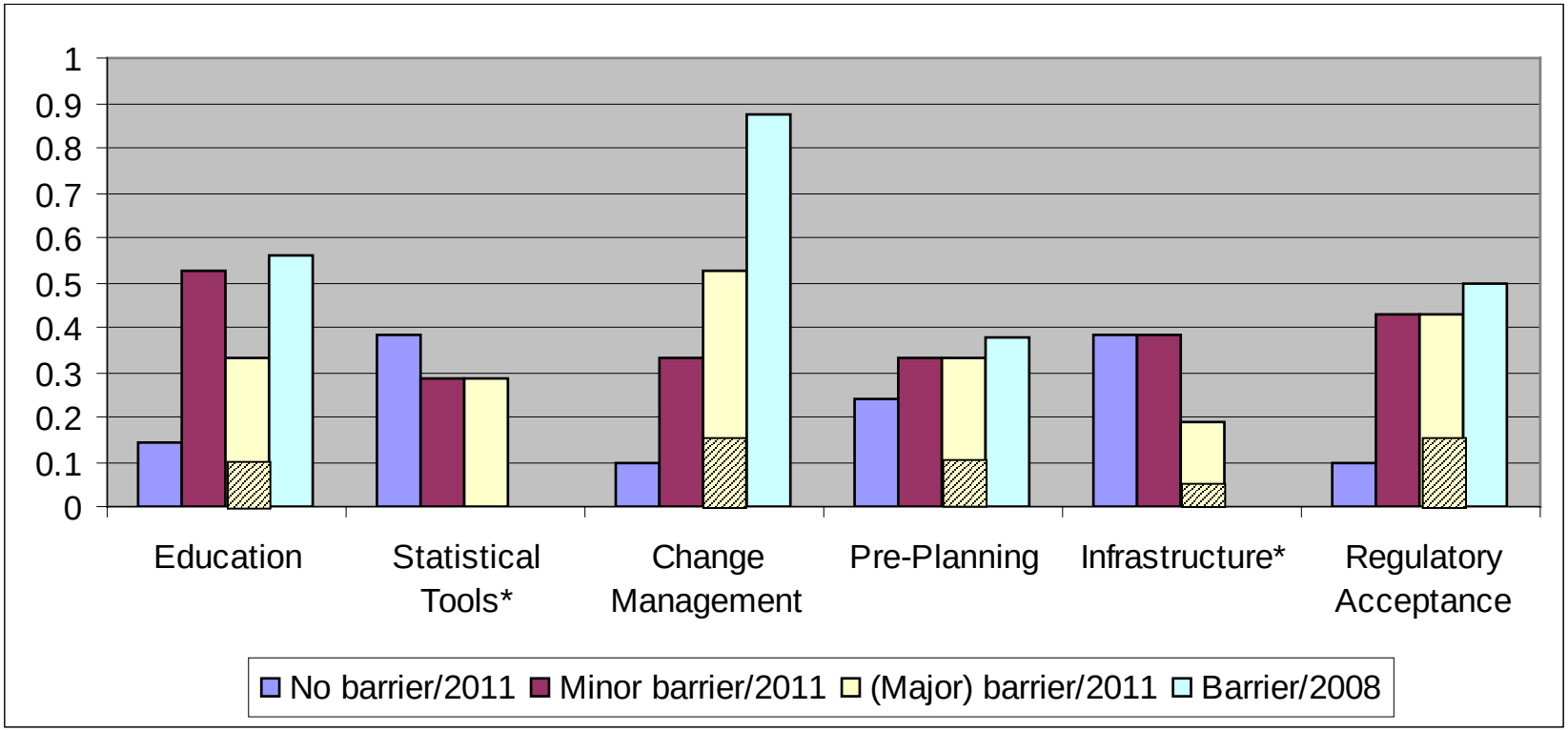
Questionnaire: AD formally considered

- *Since 2010, percentage of all trials for which AD considered* during the conception phase (regardless of whether used)*
- ** Calculations/simulations performed for comparison to more traditional designs*

- Based on responses from 12 of the 18 organizations
  - ADs (GSDs/blinded SSR/other) are considered for approx. 30% of *exploratory* trials
  - GSDs/blinded SSR are considered for approx. 40% of *confirmatory* trials
  - Other ADs are considered for approx. 25% of *confirmatory* trials

Questionnaire: Barriers

- *New/persisting barriers to ADs since the FDA draft guidelines in February 2010 (where barriers may or may not be attributed to the issuing of the guidance)*



*: Not present in 2008 Questionnaire

Note: One organisation gave four sets of answers (one per unit)

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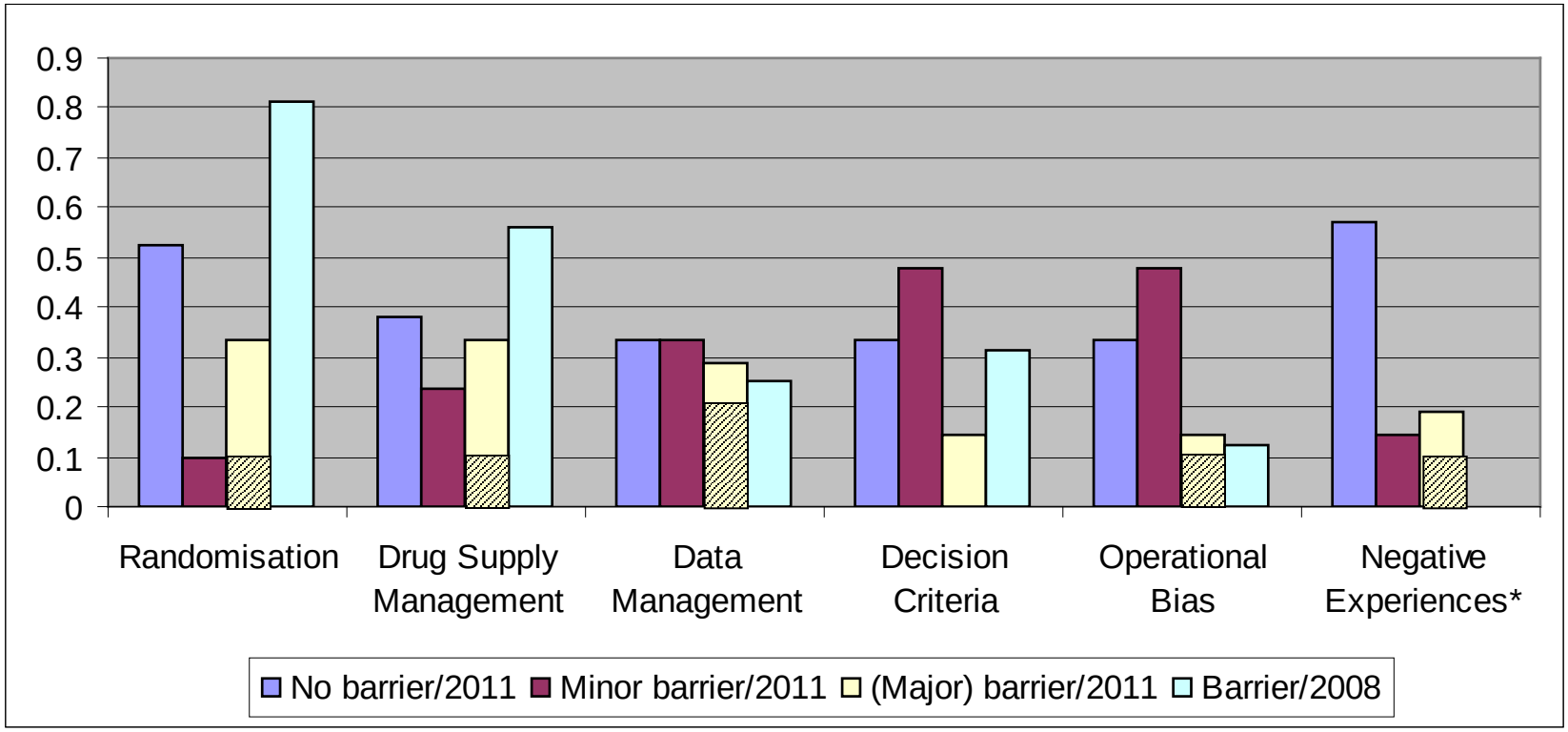

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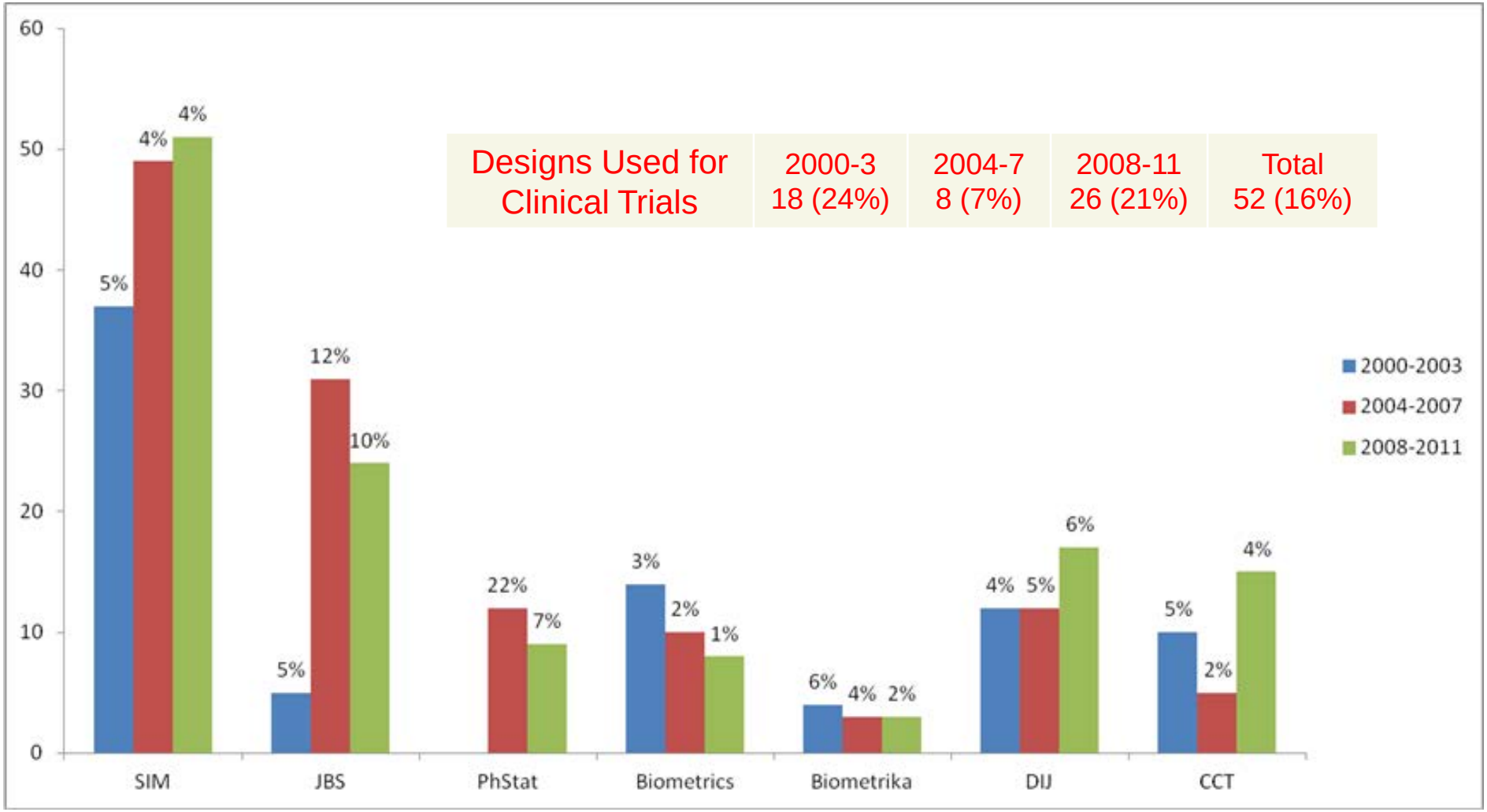
Literature Review

- 7 scientific journals reviewed from Jan 2000 to Sep 2011
  - Statistics in Medicine
  - Journal of Biopharmaceutical Statistics
  - Pharmaceutical Statistics
  - Biometrics
  - Biometrika
  - Drug Information Journal
  - Contemporary Clinical Trials (Controlled Clinical Trials before 2005)
- Key Limitation: Predominantly statistical journals referring to design methodology rather than implemented ADs

Number & Propn of Articles with ≥1 AD Search Item



Designs Used for Clinical Trials	2000-3	2004-7	2008-11	Total
	18 (24%)	8 (7%)	26 (21%)	52 (16%)

Registries Review - ClinicalTrials.gov

- Text mining with a clinical trials intelligence database, to identify at least one AD term in either the clinical trial title or treatment plan
- The number of trials identified from Jan 1996 – Sep 2011 are reported here
- Possible reasons for low numbers in 2010 and 2011:
  - reporting delays
  - delays in the identification of trials
    in the search system used

Start Year	Number of trials	Number of Trials by Year Range
1996	5	18
1997	4	
1998	6	
1999	3	
2000	7	34
2001	2	
2002	14	
2003	11	
2004	17	109
2005	24	
2006	36	
2007	32	
2008	23	55
2009	22	
2010	6	
2011	4	

Persistent Barriers – Key Messages

- Key persistent barriers to implementing AD include

➢ **Regulatory acceptance** (risk of not obtaining agency approval due to the use of an AD)

➢ **Education** (lack of team knowledge about methodology)

➢ **Pre-planning** (lack of time to conduct clinical trial simulations that are necessary for doing AD)

➢ **Change management** (team preference/greater comfort with traditional approach)

Regulatory Acceptance – is it a myth????

- What regulators really don't like is badly understood adaptive designs
  - Lack of knowledge of operating characteristics
  - What is type I error and power – control of type I error is non-negotiable
  - Dose selection – is it a company risk?
  - Pre-specified
- Ethical
  - Guided dose escalation, model based
  - Can help protect exposure to non-efficacious or unsafe doses
  - Futility stop poor drugs early
- Regulators have suggested adaptive designs when the study does not present them
- Regulators are learning as well as industry

Regulatory Acceptance – is it a myth????

- Both the FDA & EMEA are most flexible when the trial object is to explore, or “learn”.
  - Encourage adaptive designs in exploratory development
- Allow more lead time for regulatory review
  - Let the agency know that the design is adaptive, so that it will be assigned to appropriate reviewers
- Need to show that the trial is adequately designed
  - Summarize simulation results in the protocol (sample size sensitivity)
  - Phase II + studies
    - Send simulation report to agencies along the protocol
- In protocol mention who will have access to unblinded data
  - Phase II and III - Be ready to provide documentation describing firewalls

What Should be done Cross-Functionally?

- General acceptance is not a statistical thing
- Need clinical input
- Recruitment rate versus endpoint available – is it realistic?
- Statisticians can drive but without clinical, supplies, data management, regulatory it could be like driving a car with square wheels
- Senior management buy-in.
  - If senior managers do not buy in then it may be hard
- Changing the sceptic minds (“I cannot do an ASTIN”)
  - Good examples of where an adaptive design has worked
  - Simple adaptive designs – stop for futility – can we take the chance of stopping a good drug
- If I put futility in people will think I think the drug is going to fail
  - 90% of drugs fail?????
  - Plan for stopping if it does not work

Education

- General education needed around adaptive designs
- Could focus on the regulatory guidance
  - FDA Guidance is still draft
  - FDA known and not well known methods
  - Does not mean “don’t use” if it is not well known
  - EMA only deals with confirmatory
- Teams need to think about the best way to achieve an objective not just “I want to do an adaptive design”
- Could focus on types but examples are needed and these are not always apparent in a large organisation
- Learn from mistakes made
- Courses should focus on implementation not just on methods
  - It is no use having a brilliant methodology if you cannot implement it
- How much preparation time is needed?

Pre-Planning and Change Management can be covered by Education

- Course examples detail simulation
  - Planning
    - Simulations take time so plan before you act
    - Understand the methods
    - Use tools available if possible – R packages, FACTS, EAST, Addplan – also need training
  - What are the operating characteristics? Clinical define and then we simulate – present then refine
- Comparisons to traditional designs
  - Why should you use an adaptive design?
- I am happy with my traditional approach why should I change anyway? I have a comfort zone

Conclusions

- Are Adaptive Designs a FAD?
- I would suggest not given the increasing number being performed
  - Industry and academia are showing more enthusiasm for ADs
  - Rise in Exploratory ADs in recent years
- Barriers – Recommendations
  - Education has to involve all levels (including senior management) so that there is alignment on expectations
  - Regulatory agencies are generally open to discussing adaptive approaches, we recommend early engagement in discussions with regulators
- Do not see adaptive designs as a panacea for everything

Doing now what patients need next