DIA Adaptive Design Scientific Working Group

Perception and use of adaptive designs
in the industry and academia: persistent barriers and recommendations to overcome challenges

SCT Meeting 2012, Miami

Caroline Morgan, DIA ADSWG Survey Subteam

Outline

- Introduction to the Adaptive Design Scientific Working Group (ADSWG)
- ADSWG Ongoing Survey
  - Objectives
  - Methods and Key Limitations
  - Currently Available Results
    - Questionnaire
    - Literature Review
    - Registries Review
- Conclusions
- Persistent Barriers and Recommendations

DIA ADSWG History & Objective

Adaptive Design Working Group (ADWG) started in 2001

- Working in association with PhRMA until 2011
- Transferred to DIA as a Scientific Working Group (SWG) in 2011 and became the ADSWG

Objective: To ensure that ADs are a well understood, accepted, and broadly utilized approach (where and when applied appropriately) in clinical research

ADSWG is organised & run by a dedicated group of volunteers

ADSWG Core Committee and Subteams

Brenda Gaydos, ADSWG Core Committee Chair

Subteams:

Key Opinion Leader Lectures
Chair: José Pinheiro, Johnson & Johnson
Co-Chair: Weili He, Merck
Co-Chair: Judith Quinlan, Aptiv Solutions

Trial Simulation
Chair: Brenda Gaydos, Eli Lilly

Material Supply
Chair: Nancy Burnham, GSK
Co-Chair: Judith Quinlan, Aptiv Solutions

DMC
Chair: Paul Gallo, Novartis

Personalized/Precision Medicine
Chair: Sandeep Menon, Pfizer
Co-Chair: Michael Krams, Johnson & Johnson

Adaptive Trials at the Portfolio Level
Chair: Nitin Patel, Cytel
Co-Chair: Zoran Antonijevic, Quintiles

Communications
Chair: Teresa Perney, Roche
Co-Chair: Olga Marchenko, Quintiles

Survey
Chair: Caroline Morgan, Cytel

ADSWG Survey Subteam Members

Chair: Caroline Morgan, Cytel

Members:

Alun Bedding, GSK

Li Chen, Amgen

Christopher Coffey, University of IOWA

Brenda Gaydos, Eli Lilly

Susan Huyck, Merck

Martin Jenkins, AstraZeneca

Silke Jörgens, Aptiv Solutions

Lingyun Liu, Cytel

Jeff Maca, Novartis

Daniel Meyer, Pfizer

Nitin Patel, Cytel

Teresa Perney, Roche

Yili Pritchett, Abbott

Judith Quinlan, Aptiv Solutions

William Wang, Merck

J. Kyle Wathen, J&J

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 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

Results compiled in central DB by Elizabeth Zahn, UIOWA

Compared to results from previous survey (PhRMA ADWG)

- 13 medium to large pharma companies + 3 CROs
- Case studies of ADs designed/conducted from 2003-2008

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 organisation in 2011
  - 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 Definition

A clinical study design that uses accumulating data to decide whether and how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial

Note 1: Only trials with pre-planned adaptations were reported in the questionnaire.

Note 2: Standard 3+3 designs were not to be considered as ADs for the purposes of the questionnaire.

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 reestimation, 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 reestimation).

Questionnaire: Exploratory/Confirmatory

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

GSDs/blinded SSR:
283 studies

Other ADs:
153 studies

Other ADs

2011 Survey

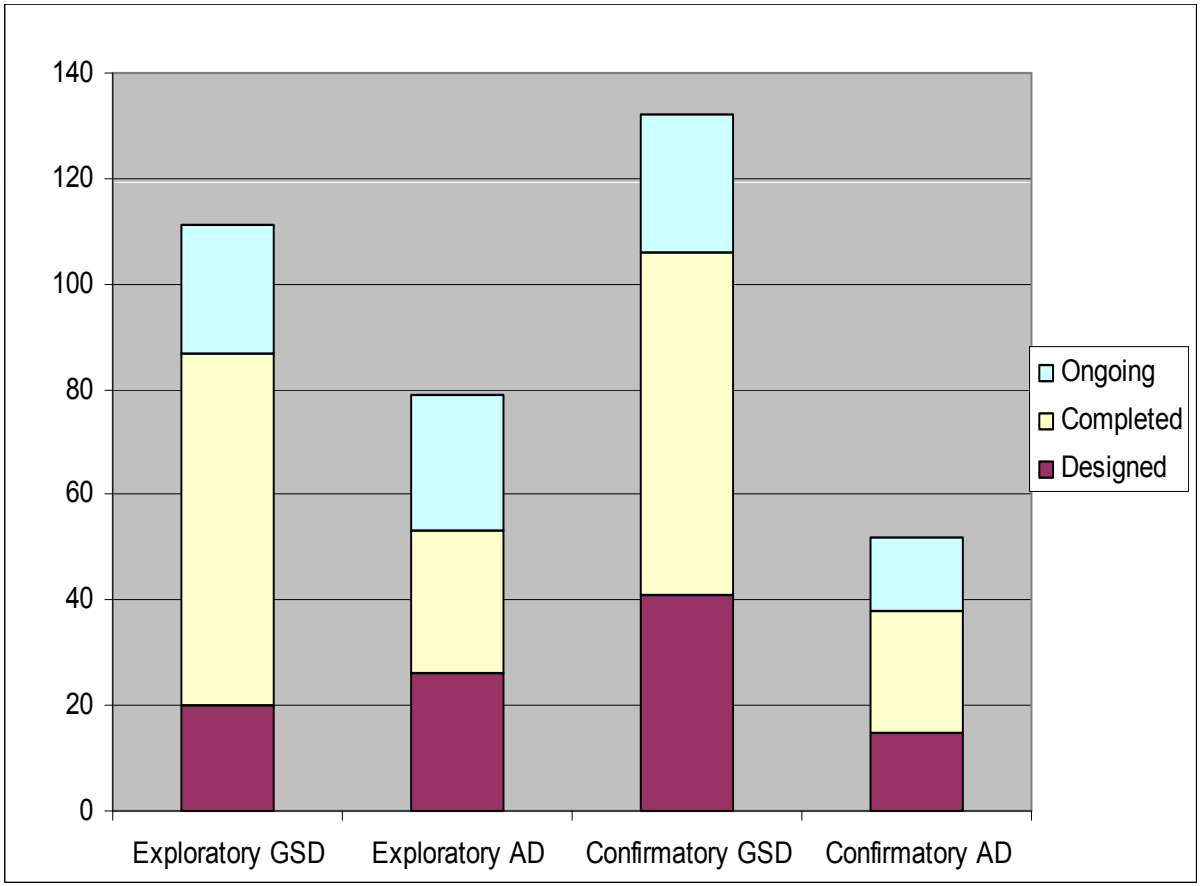
100/153 exploratory

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)*

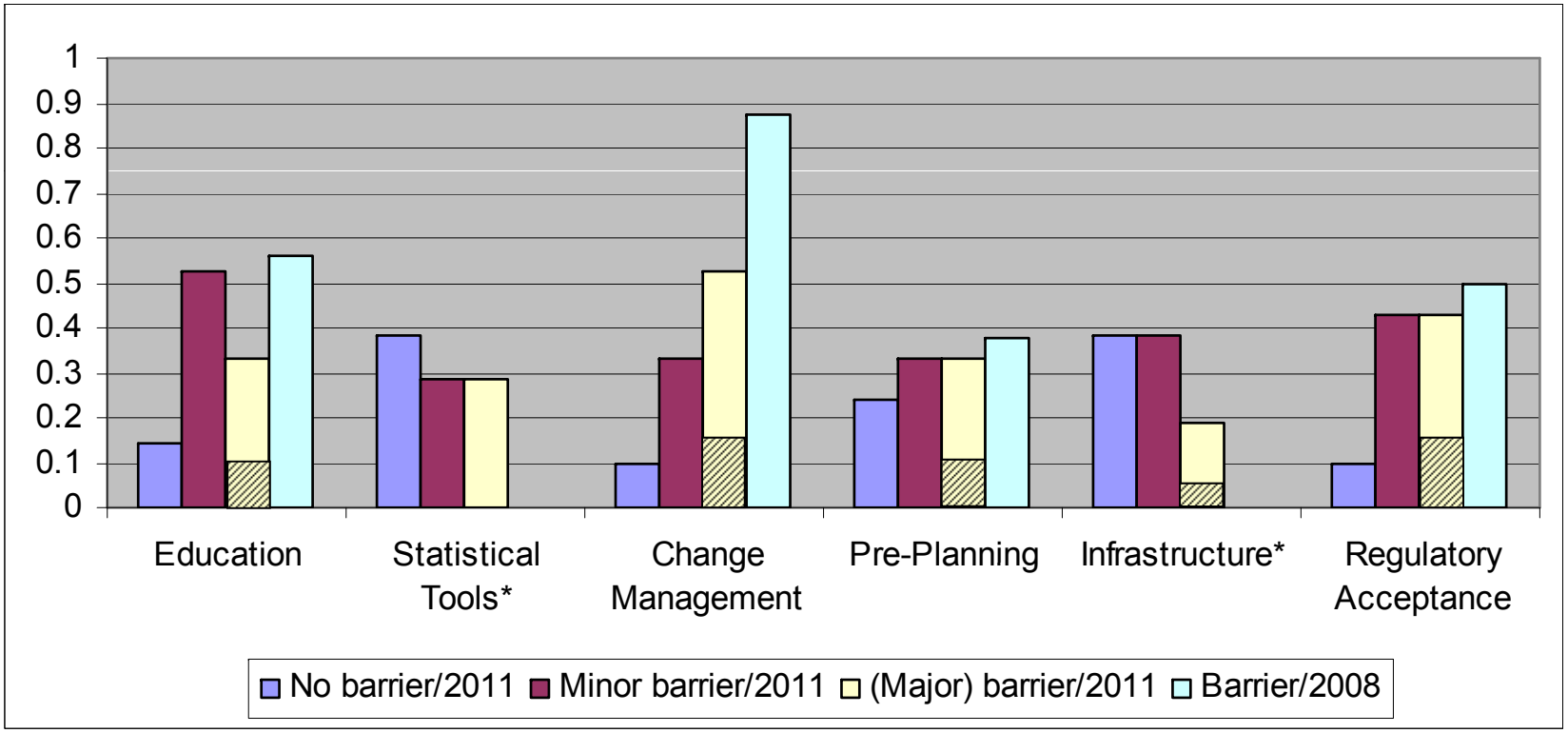
* *Calculations/simulations performed for comparison to more traditional designs*

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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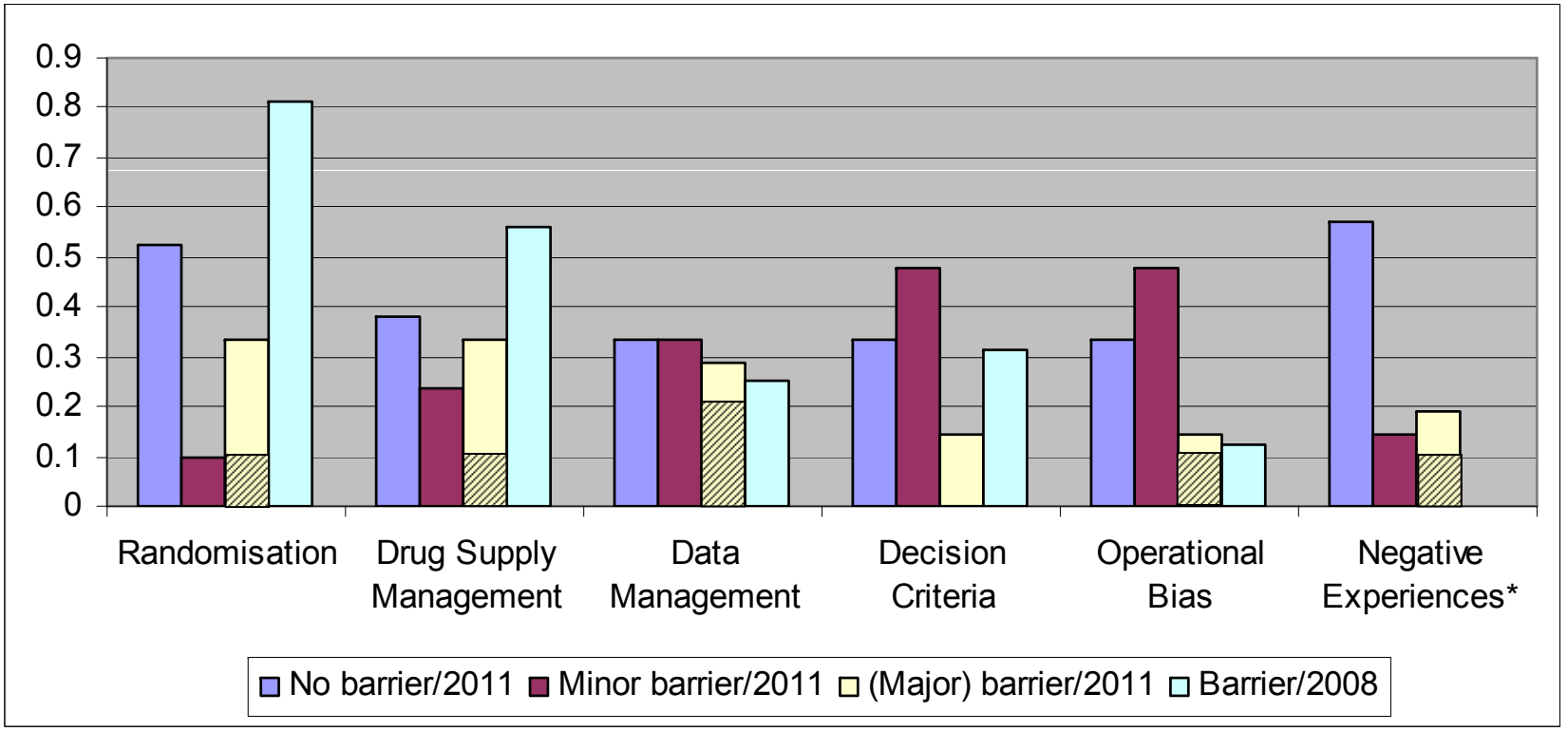


*: Not present in 2008 Questionnaire

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

Questionnaire: Specific AD working groups

Of the 18 participants, 13 have some form of AD working group in place

- 7 of the 11 pharma/biotechs
- All of the 6 CROs

Questionnaire: Bayesian Methodology

Bayesian methodology...

- Has been used in at least one exploratory trial (n=12)
- Has been used in at least one confirmatory trial (n=3)
- Has been used in at least one confirmatory trial for a primary analysis (n=1)
- Has not been used in any clinical trials (n=8)

Note: One organisation gave four sets of answers (one per unit) and one organisation did not respond

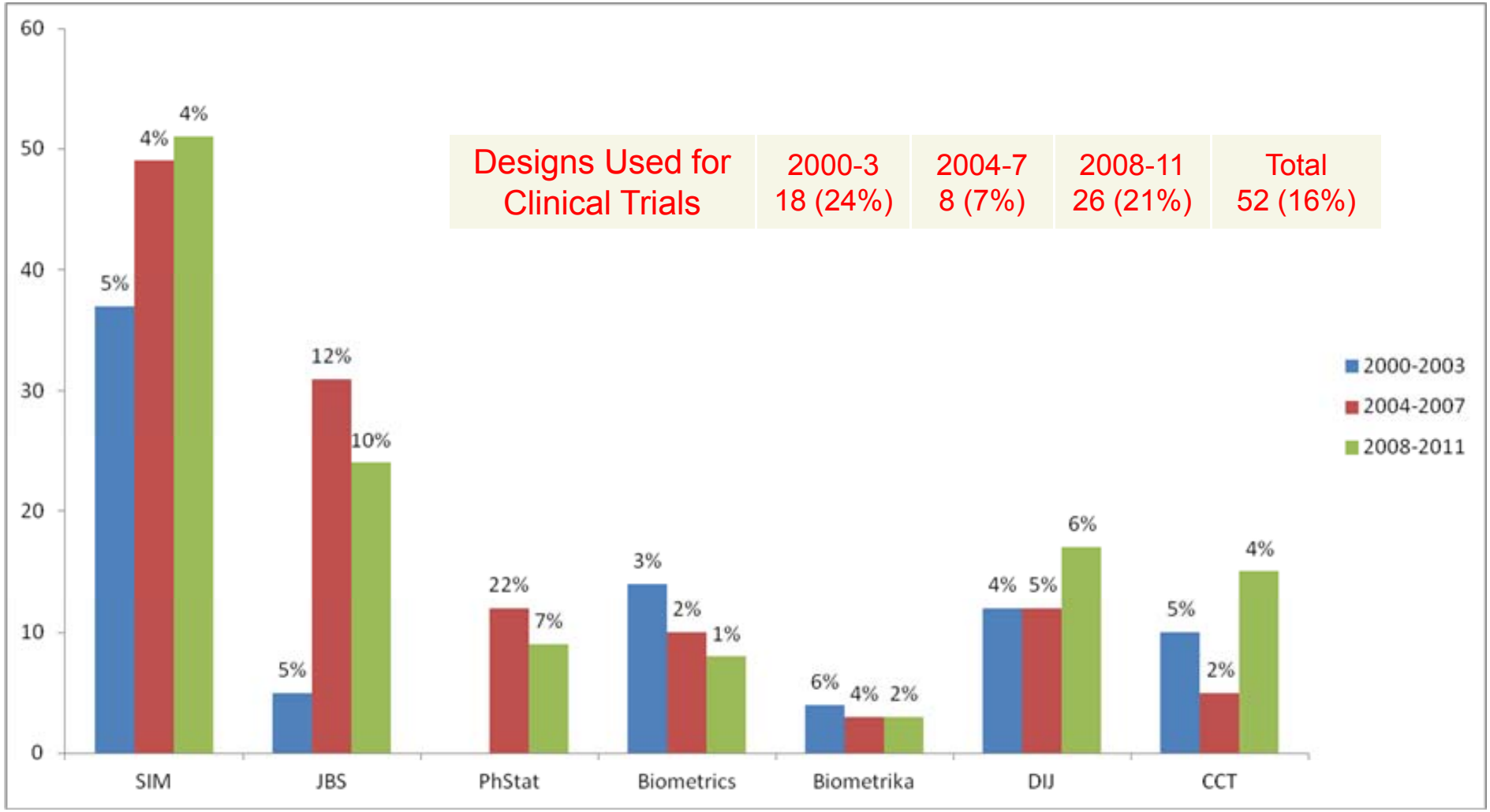
Literature Review

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%)

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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	

Conclusions

- Industry and academia are showing more enthusiasm for ADs
- Rise in Exploratory ADs in recent years

  FDA Draft Guidance on ADs encourages the use of "less well-understood methods" in exploratory studies
- Most common AD types: Treatment group adaptations (e.g. dose selection) and early stopping for futility
- Limited use of Bayesian methodology

  More common in exploratory phases, particularly in recent years
- Some AD barriers identified in the 2008 survey now less common

  e.g. reduction of barriers due to the increased availability of flexible randomisation and drug supply systems

Persistent Barriers

Key persistent barriers to implementing AD include

- **Education** (lack of team knowledge about methodology)
- **Change management** (team preference/greater comfort with traditional approach)
- **Pre-planning** (lack of time to conduct clinical trial simulations that are necessary for doing AD)
- **Regulatory acceptance** (risk of not obtaining agency approval due to the use of an AD)

Recommendations

Recommendations to overcome these challenges

- Education has to involve all levels (including senior management) so that there is alignment on expectations
- Additional time spent on simulation guided clinical trial design ultimately results in higher information value and increases chance of trial success
- Regulatory agencies are generally open to discussing adaptive approaches, we recommend early engagement in discussions with regulators