DIA Adaptive Designs Scientific Working Group Survey Results

Alan Hartford, AbbVie

September 27, 2017

DIA Adaptive Designs Scientific Working Group (ADSWG)

ADSWG Mission: Ensure that adaptive designs, when applied appropriately, are an accepted and broadly utilized approach that leads to improved drug development and patient care. (Chair: Bob Beckman)

Several subteams

- For specific disease areas such as neuropathic pain and oncology
- For commenting on draft guidances
- For training and KoL Series
- For specific types of ADs such as SSR and precision medicine
- For best practices
- **For generating and reporting surveys**

DIA ADSWG Survey Subteam

For generating and reporting surveys to inform on the perception and use of ADs for use for drug and biologics development.

Have ADs become more commonplace?

Have specific adaptations become more accepted or useful?

Are there still barriers to designing or implementing clinical studies with adaptations?

DIA ADSWG Survey Team for Drugs and Biologics

Alan Hartford, AbbVie (Chair of Survey Team)

Mitchell Thomann, Eli Lilly

Xiaotian Chen, AbbVie

Eva Miller, INC Research/inVentiv Health

Alun Bedding, Roche

Silke Jörgens, ICON plc

Lingyun Liu, Cytel

Li Chen, Amgen

Caroline Morgan, Cytel

Names in blue – provided specific content to slides.

Components of the Survey Team's Effort

Survey

Literature Review

Registry Review (no time to discuss today)

ADSWG Survey Team Efforts

Timetable

	2008 Effort	2012 Effort		2016 Effort	
	Survey	Survey	Literature and Registry Reviews	Survey	Literature and Registry Reviews
2000-2003			X		X
2004-2007	X*		X		X
2008-2011***		X**	X		X
2012-2015				X	X

*For the 2008 effort, survey spanned Jan 2003 – March 2008.
** The 2012 Survey spanned Jan 2008 to only Sep 2011.
*** The FDA Draft Guidance for Industry, Adaptive Design Clinical Trials for Drugs and Biologics released February 2010
Note: the 2008 and 2012 surveys included devices but only the respondents of the 2008 survey provided device AD information.

Design of Survey

There were 10 questions and most had multiple parts.

Quick summary of questions covered:

- How many trials with ADs and what are the specific adaptations used?
- To what extent have Bayesian methodologies been used in ADs?
- What barriers exist to using ADs?
- Do organizations have any AD working groups?
- Has the perception/use of ADs changed in organizations?
- To what extent were ADs used in exploratory vs. confirmatory trials?
- To what extent have the management of AD trials been outsourced?

Question 2 (deleted due to inability by most to respond)

Please provide the number and approximate percentage of trials for which an AD was considered at some point during the conception phase, regardless of whether or not it was chosen as the final design, between 1st January 2012 and 31st December 2015.

The fields should be exclusive (the sum of all fields should equal the total number of clinical trials designed in your organisation for which an AD was considered at some point during the conception phase).

Number and %[1] of trials for which:	Exploratory	Confirmatory
Only GSDs / blinded SSR with no other form of adaptation were considered	____ (____%)	____ (____%)
Other ADs were considered	____ (____%)	____ (____%)

1. Approximate percentage over all clinical trials designed in your organisation between 1st January 2012 and 31st December 2015

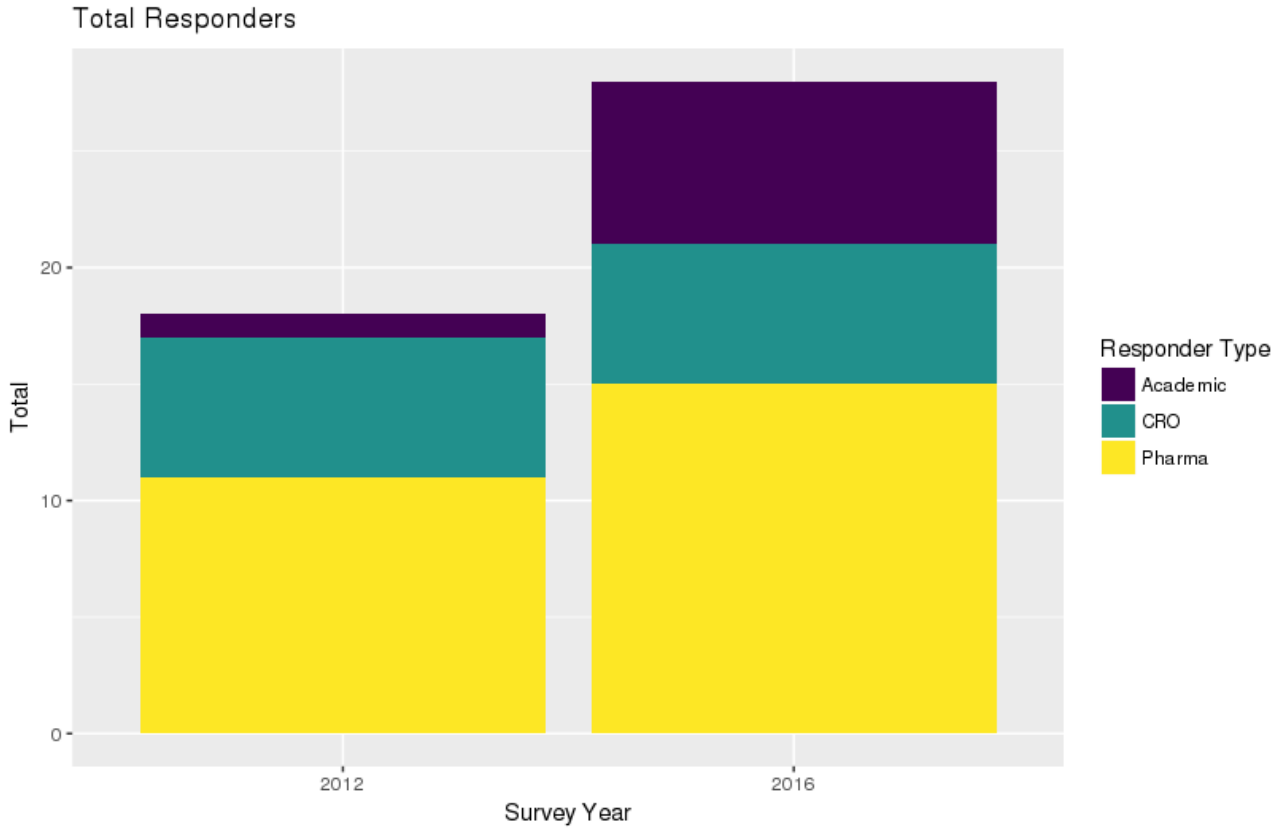
To whom did we send the survey?

In 2012, sent to 92 organizations including biopharmaceutical, CRO, and academic institutions.

After finding additional contact info, we sent the 2016 survey to a total of 114 institutions via email

We thank the ASA Biopharmaceutical Section for use of their Gold Membership with Surveymonkey.

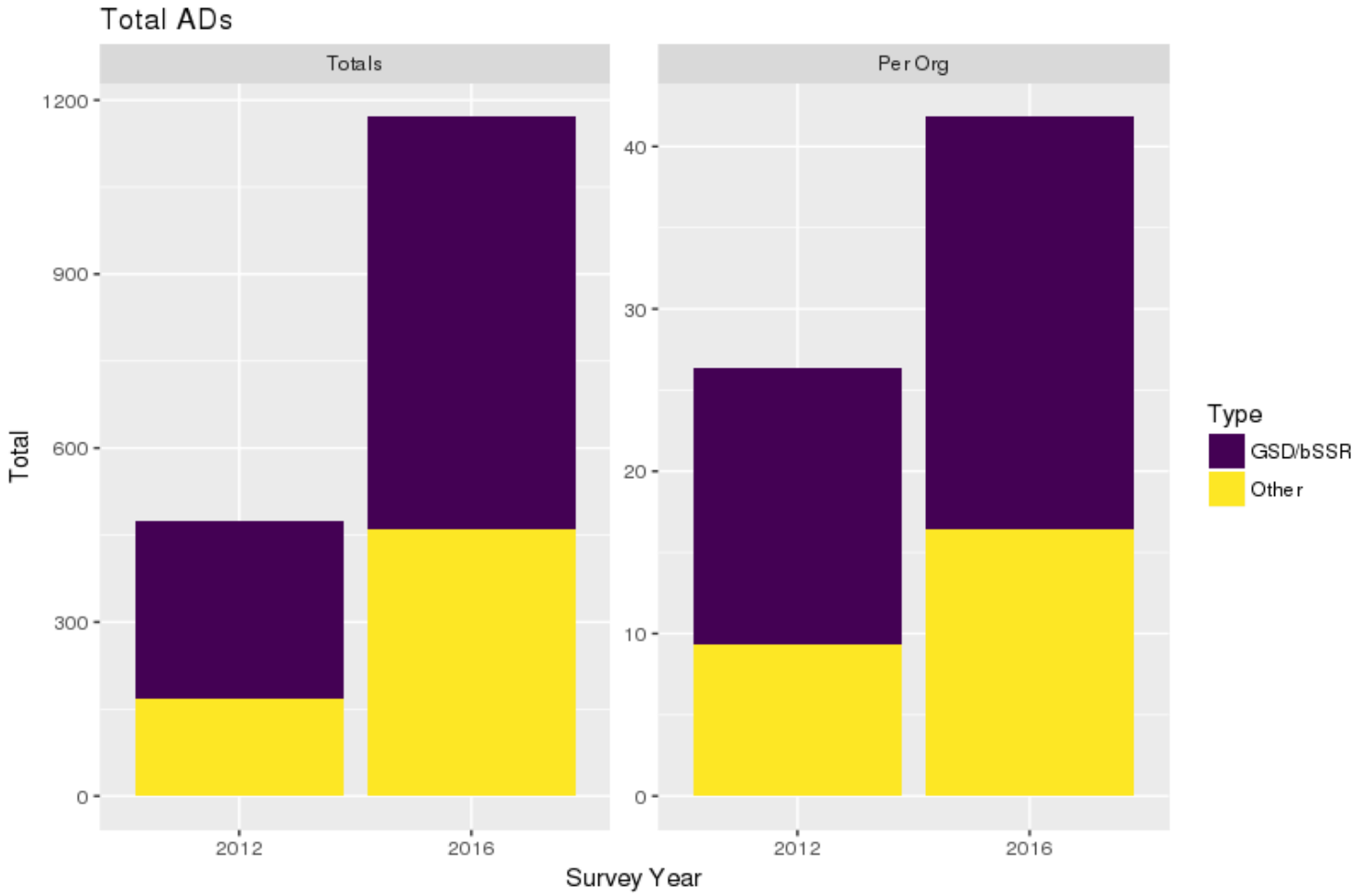
Respondents



Type	2012	2016
Pharma	11	15
CRO	6	6
Academic	1	7
Total	18 (17*)	28 (25*)

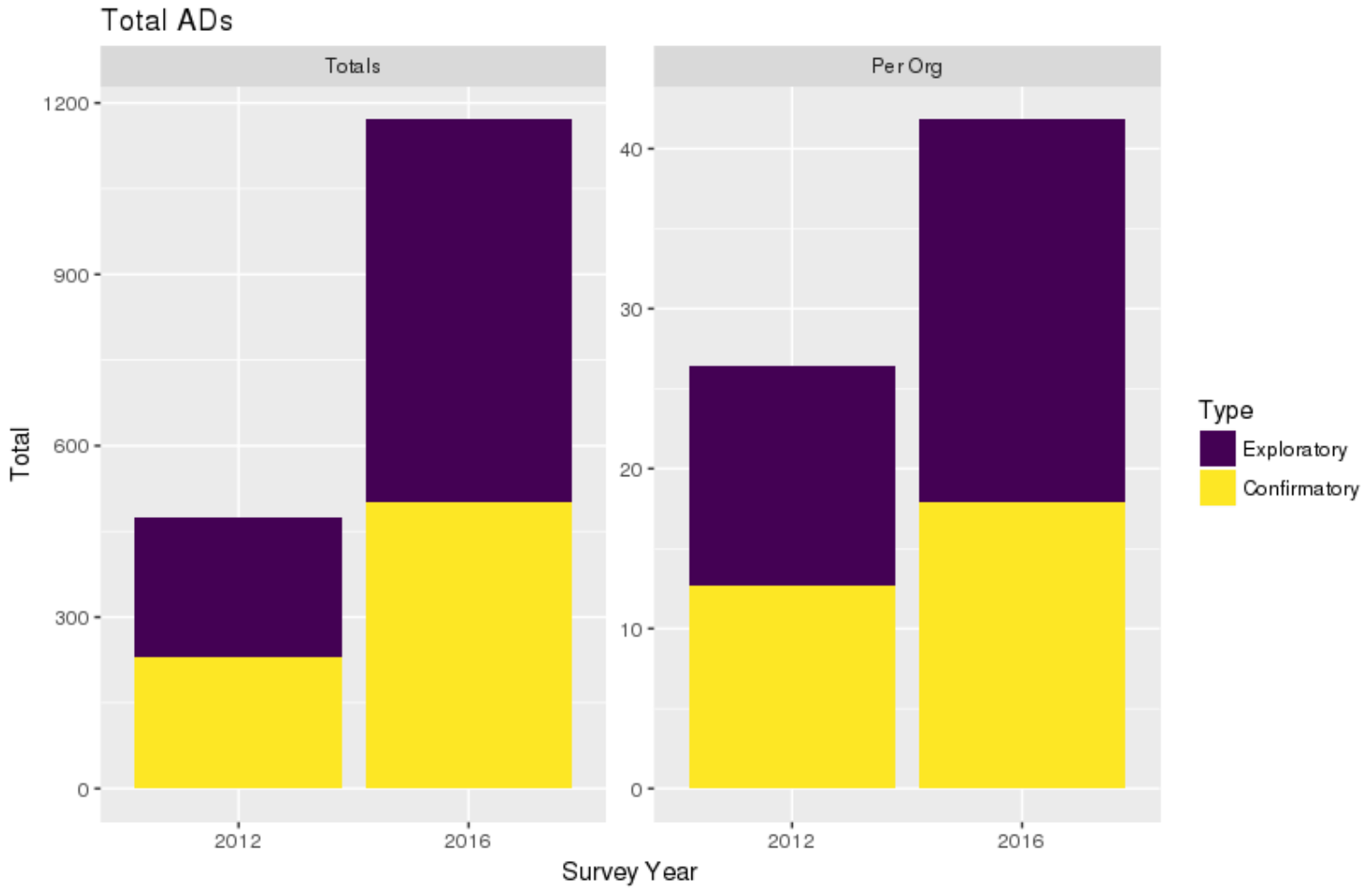
* Provided total number of ADs

Total ADs Reported



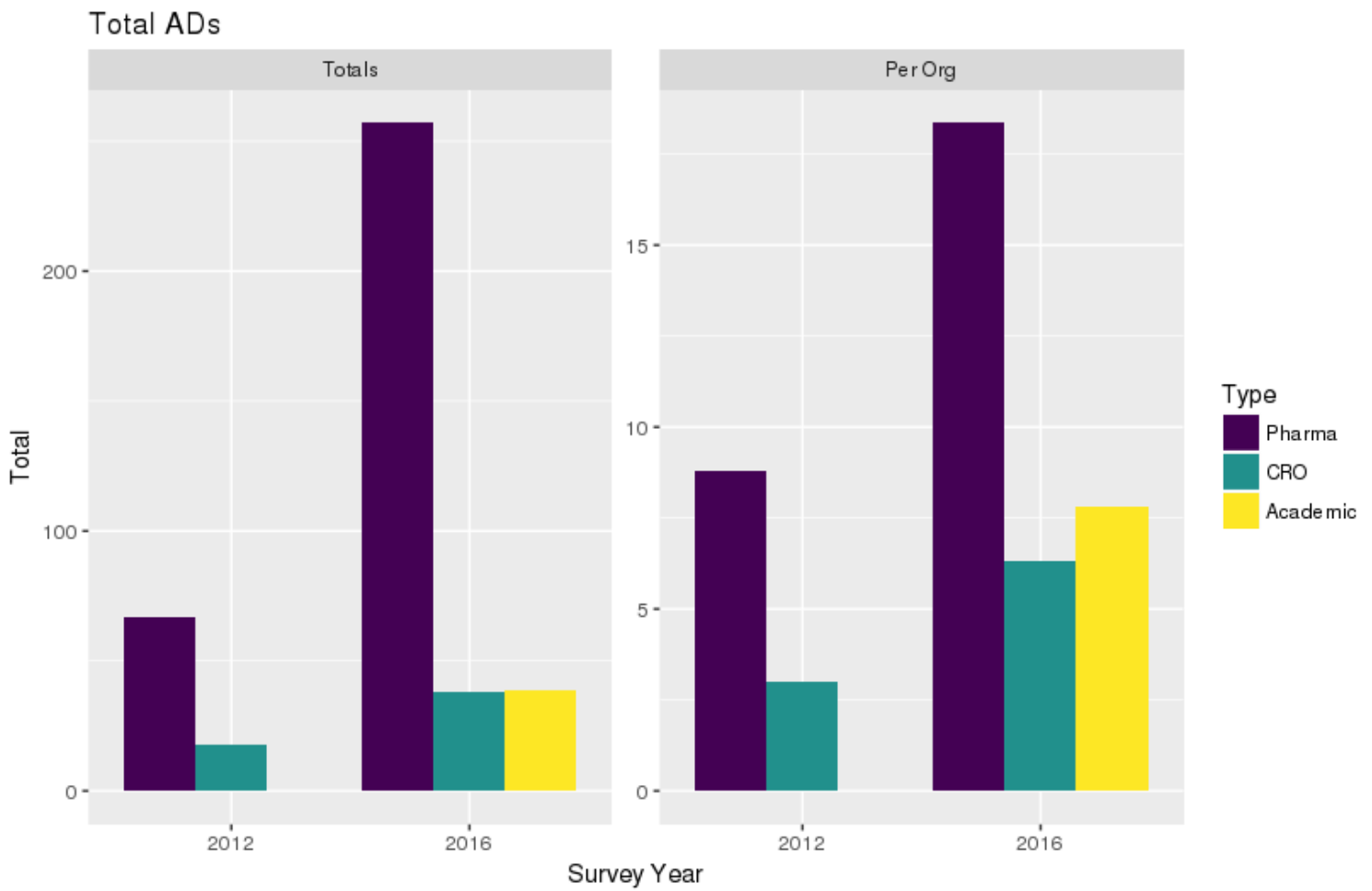
Type	2012	2016
GSD/bSSR (% of Total)	307 (65%)	712 (61%)
Other (% of Total)	168 (35%)	459 (39%)
Total (ADs/Org.)	475 (27.9)	1171 (46.8)

Total ADs Reported



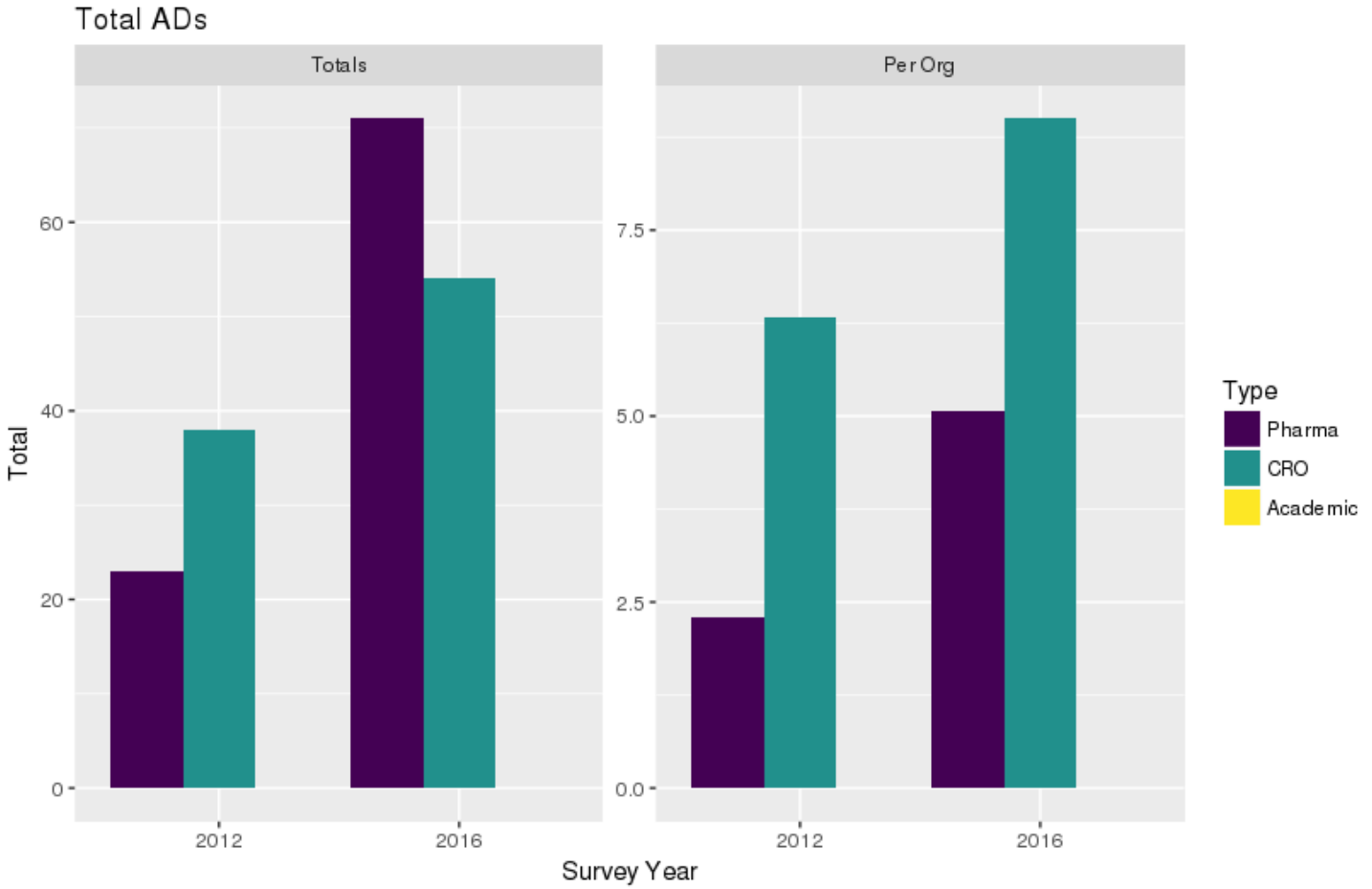
Type	2012	2016
Exploratory (% of Total)	246 (52%)	669 (57%)
Confirmatory (% of Total)	229 (48%)	502 (43%)
Total (number of ADs/Org.)	475 (27.9)	1171 (46.8)

Other ADs - Exploratory



Type	2012	2016
Pharma (% of Total)	88 (83%)	257 (77%)
CRO (% of Total)	18 (17%)	38 (11%)
Academic (% of Total)	0	39 (12%)
Total (ADs/Org.)	106 (6.2)	334 (13.4)

Other ADs – Confirmatory



Type	**2012**	**2016**
Pharma (% of Total)	23 (38%)	71 (57%)
CRO (% of Total)	38 (62%)	54 (43%)
Academic (% of Total)	0	0
Total (ADs/Org.)	61 (3.6)	125 (5.0)

Most Common “Other ADs”

Type	2012	2016
Treatment Group Selection	72 (55%)	123 (24%)
Unblinded SSR	52 (40%)	98 (19%)
Randomization Ratio	18 (14%)	52 (10%)
Population	3 (2%)	66 (13%)

Note that 18 of the 66 population adaptive trials in 2016 were from one company for HCV trials.

See our upcoming paper for breakdowns within exploratory and confirmatory subgroups.

Bayesian Designs

2012

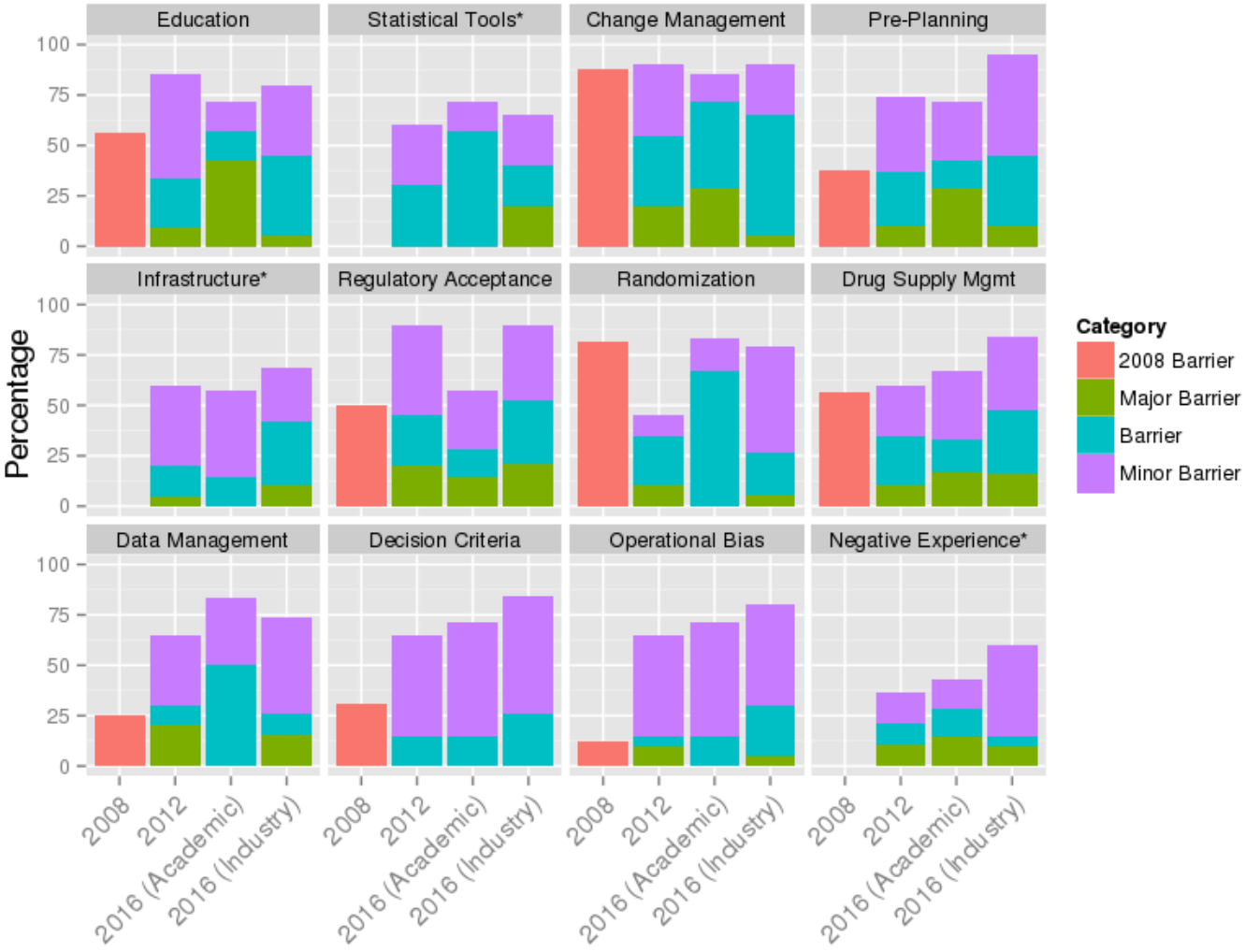
- Orgs. reporting Bayesian usage:
  - 9 – Exploratory (56%)
  - 2 – Confirmatory Interim (13%)
  - 1 – Confirmatory Primary Analysis (6%)

2016

- Orgs. reporting Bayesian usage:
  - 18 – Exploratory (78%)
  - 8 – Confirmatory Interim (35%)
  - 2 – Confirmatory Primary Analysis (9%)

The number respondents to this question: 16 in 2012 and 23 in 2016.

Perception of barriers to AD usage in clinical trials



Literature Search: Keywords

18 key words used, 12 of which were used in the previous effort (2012).

The literature search was performed using a careful manual review by (quickly) reading all papers found using the key word search.

One specific challenge of the manual review was to specify if clinical trials were exploratory, confirmatory, both, or unknown.

Key Words (N=12 and N=18)

- Adaptive Design
- Flexible Design
- Innovative Design
- Seamless Design
- Group Sequential
- Interim Analysis
- Interim Monitoring
- Sample Size Re-Estimation
- Sample Size Re-Assessment
- Adaptive Dose Finding
- Adaptive Randomization
- Population Enrichment
- Response Adaptive*
- Early Stopping*
- Stopping Boundary*
- Adaptive Dose Escalation*
- Adaptive Treatment Selection*
- Continual Re-Assessment Method (and "CRM and Reassessment")*

Note: Spelling variations were included as appropriate.

Note: * indicates new search terms in addition to the 12 search terms used in 2012 literature and registry review

Number of articles identified using 12 keywords

Type of Journal	2012-2015	2000-2015
Statistical	224	560
Methods or Position Papers	174	444
Case Studies	50	116
Clinical	58	121

Case Studies in statistical and clinical literature of most interest.

Search engines: Medline, Biosis, Embase, and Embase Alert

Statistical Journals (N=8): Biometrics, Biometrika, Contemporary Clinical Trials (formerly Controlled Clinical Trials), Therapeutic Innovation & Regulatory Science (formerly Drug Information Journal), Clinical Trials, Journal of Biopharmaceutical Statistics, Pharmaceutical Statistics, and Statistics in Medicine.

Medical Journals (N=5): British Medical Journal, Journal of the American Medical Association, Lancet, Lancet Neurology and New England Journal of Medicine.

Trends Shown by Literature Review – Early Stopping

Increasing number of papers showing methodology and use of early stopping rules for efficacy, futility, and safety only.

	2000-2003		2004-2007		2008-2011		2012-2015		Total	
	STAT	MED	STAT	MED	STAT	MED	STAT	MED	STAT	MED
For Efficacy	22 (39%)	12 (80%)	22 (33%)	20 (80%)	29 (24%)	21 (91%)	103 (47%)	46 (79%)	176 (31%)	99 (82%)
For Futility	18 (32%)	7 (47%)	26 (39%)	10 (40%)	24 (20%)	10 (43%)	97 (44%)	24 (41%)	165 (29%)	51 (42%)
For Safety Only	2 (4%)	0 (0%)	0 (0%)	0 (0%)	4 (3%)	0 (0%)	49 (22%)	6 (10%)	55 (10%)	6 (5%)

Trends Shown by Literature Review – Other ADs and Bayesian

Increasing number of papers report methodology and use of ADs and Bayesian designs.

	2000-2003		2004-2007		2008-2011		2012-2015		Total	
	STAT	MED	STAT	MED	STAT	MED	STAT	MED	STAT	MED
Treatment Group	8 (14%)	0	17 (25%)	1 (4%)	29 (24%)	0	69 (31%)	5 (9%)	123 (22%)	6 (5%)
Random. Ratio	5 (9%)	0	9 (13%)	3 (12%)	21 (17%)	0	57 (26%)	8 (14%)	92 (16%)	11 (9%)
Population	0 (0%)	0	1 (1%)	0	5 (4%)	0	33 (15%)	0 (0%)	39 (7%)	0
Endpoint	1 (2%)	0	0	0	3 (2%)	0	24 (11%)	3 (5%)	28 (5%)	3 (2%)
Bayes	4 (5%)	0	15 (12%)	0	20 (15%)	0	80 (36%)	1 (2%)	119 (21%)	1 (1%)

Trends Shown by Literature Review – Sample Size Re-estimation

Increasing number of papers report methodology and use of sample size re-estimation.

	2000-2003		2004-2007		2008-2011		2012-2015		Total	
	STAT	MED	STAT	MED	STAT	MED	STAT	MED	STAT	MED
Blinded	7 (12%)	0 (0%)	3 (4%)	0 (0%)	9 (7%)	2 (9%)	22 (10%)	5 (9%)	41 (7%)	7 (6%)
Unblinded	13 (23%)	0 (0%)	14 (21%)	0 (0%)	14 (12%)	1 (4%)	51 (23%)	2 (3%)	92 (16%)	3 (2%)

Summary

Both the survey and the literature review have shown increasing use of ADs in the development of drugs and biologics.

Perception of barriers to the usage of ADs seems to have increased slightly as more experience has been gained, i.e., we have a better understanding of where the difficulties lie.

The registry review is more complicated due to expected delay of reporting and will be summarized in our paper.

The survey results report the adaptive designs in **studies designed** during the four-year time periods.

The literature review reports **designs appearing** in papers published during the four-year time periods.

The registry review reports adaptive designs in **studies** that were **started** in the four-year time periods.

So the findings are limited as to how the results can be compared across the survey, literature review, and registry review.