

Clinical Trial Complexity

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The Typical Protocol in 2012

- **13 endpoints – 1 primary and 5 ‘key’ secondary**
- **167 procedures**
 - **85 procedures support primary and key secondary endpoints**
- **35 inclusion and exclusion criteria and 169 case report form pages**
- **Requires study volunteers to make 11 visits over an average of 175 days**

Rising Protocol Complexity and Burden

(All TAs, All Phases)

	00 – 03	04-07	08-11
Unique procedures per protocol (median)	20.5	28.2	30.4
Total procedures per protocol (median)	105.9	158.1	166.6
Total investigative site work burden (median units)	28.9	44.6	47.5
Total eligibility criteria	31	38	35
Median number of CRF pages per protocol	55	180	169

Getz et al. *Variability in Protocol Design Complexity by Phase and Therapeutic Area*. *DIJ* 2011 45(4); 413-420.

Phase II and III Study Execution 2012

	Overall	Phase II	Phase III
Number of Countries	27	18	34
Number of sites	130	42	196
Number of Patients Screened	882	287	1,300
Number of Patients Randomized	437	226	597
Number of Data Points Collected*	618,557	378,447	929,203

Source: Tufts CSDD; *Medidata

Impact of Protocol Complexity on Trial Performance

(All TAs, Phases II-III)

	Less Complex	More Complex	Difference
Study volunteer screen to completion rate	56%	23%	Halved
Time from Protocol Ready to FPFV (median)	115 days	129 days	+12%
Time from Protocol Ready to LPLV (median)	413 days	714 days	+73%
Number of Amendments	1.9	3.2	+68%

Getz et al. Assessing the Impact of Protocol Design Change on Clinical Trial Performance. *AJT* 2008 15(5); 450 - 457

Protocol Amendment Prevalence

Protocol Phase	Number of Amendments*	Number of Changes per Amendment
Phase I	2.0	5.6
Phase II	2.6	6.8
Phase III	3.6	8.5
Phase IIIb/IV	2.3	8.3
ALL PROTOCOLS	2.4	6.9

*Analysis of those protocols with at least one amendment

Note: All values are means

- 69% of all protocols have at least one amendment
- 46% of all amendments occur **BEFORE** first patient first dose
- 37% are considered 'somewhat' or 'completely' avoidable
- Adds 61-days and cost \$450,000+ to implement each amendment

Getz et al. *Measuring the Incidence, Causes and Repercussions of Protocol Amendments*. *DIJ* 2011 45(3); 265 - 275

Is Complexity Meaningful?

Core

- Procedures supporting primary and/or secondary objectives
- Procedures supporting primary, *key* secondary and safety endpoints

Non-Core

- Procedures supporting tertiary and exploratory objectives and endpoints
- Procedures supporting *supportive* secondary and exploratory endpoints
- Safety and efficacy procedures that are not included as an endpoint or objective
- Procedures not tied to an endpoint or objective

Required - GCP Compliance

- Screening requirements
- Informed Consent
- Drug dispensing (compliance)

Standard Procedures

- Performed in all trials: concomitant medications, demographics, adverse event assessment etc...

Getz, Stergiopoulos, Marlborough et al. *Quantifying the Magnitude and Cost of Extraneous Protocol Data*. AJT 2012, In Press



Distribution of Procedures by CSR/Analysis Plan Classifications...

	TOTAL PROCEDURES	
	N=25,103	
CORE	92	50.0%
REQUIRED	17	9.2%
STANDARD	34	18.5%
NON-CORE	41	22.3%
	184	

* All values are means and reflect total procedures performed per patient per protocol and the sum of the total direct procedure costs for all patients receiving protocol procedures per scheduled visit

Getz, Stergiopoulos, Marlborough et al. *Quantifying the Magnitude and Cost of Extraneous Protocol Data*. AJT 2012, In Press

... Distribution of, and Total, Direct Cost per Classified Protocol Procedures

	TOTAL PROCEDURES		TOTAL DIRECT COSTS	
	N=25,103		N=16,607	
CORE	92	50.0%	\$2.9 Million	47.9%
REQUIRED	17	9.2%	\$1.3 Million	21.7%
STANDARD	34	18.5%	\$0.8 Million	12.5%
NON-CORE	41	22.3%	\$1.1 Million	17.9%
	184		\$6.1 Million	

* All values are means and reflect total procedures performed per patient per protocol and the sum of the total direct procedure costs for all patients receiving protocol procedures per scheduled visit

Getz, Stergiopoulos, Marlborough et al. *Quantifying the Magnitude and Cost of Extraneous Protocol Data*. AJT 2012, In Press

Distribution and Cost of Procedures by Endpoint Classification and Phase

	Phase II	Phase III
Percent of Total Procedures per Study		
Non-Core	18%	25%
Required	8%	10%
Total Direct Cost per Study		
Non-Core	\$275,000 (13%)	\$1,734,000 (18%)
Required	\$334,000 (16%)	\$2,210,000 (24%)

Getz, Stergiopoulos, Marlborough et al. *Quantifying the Magnitude and Cost of Extraneous Protocol Data*. AJT 2012, In Press

Q&A and THANK YOU!

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