Building Quality into Clinical Development: Outsourcing

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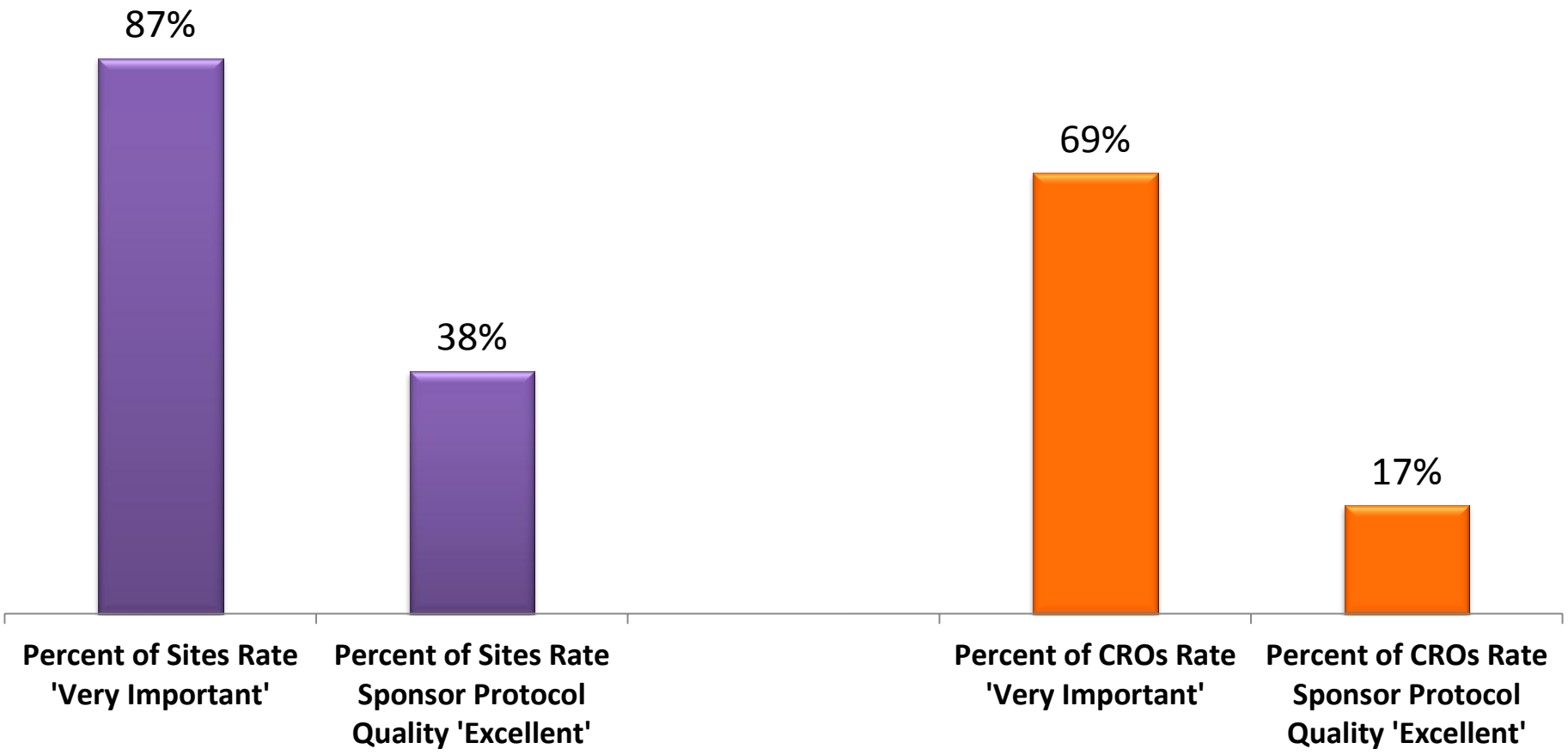
Topline Thoughts

- **QRM and QbD an initiative to exert more QA/QC control and oversight or to sustainably improve patient safety and data integrity while streamlining performance and increasing success rates?**

- **It's not just about operating process measurement and control: It must target root cause(s) of the problem – PLANNING PROCESS THAT GUIDES OPERATING PROCESSES**
  - **Primary means to build quality rests fundamentally with improvements in protocol design process**

- **Top down approach (e.g., agencies and sponsors) is out of touch with emerging realities of drug development: Better to use a more collaborative approach that leverages best positioned parties (CROs and Investigative Sites).**

A Wide Gap Between Importance of Protocol Design and Quality of Protocol



Source: CenterWatch surveys of sites (N=3,209) and CROs (N=134), 2011

Rising Protocol Complexity and Burden

(All TAs, All Phases)

	'01 '04	'05 '08	Difference
Unique procedures per protocol (median)	20.5	28.2	+38%
Total procedures per protocol (median)	105.9	158.1	+49%
Total investigative site work burden (median units)	28.9	44.6	+54%
Total eligibility criteria	31	49	+58%
Number of case report form pages per protocol (median)	55	180	+227%

Getz et al. Assessing the Impact of Protocol Design Change on Clinical Trial Performance.
American Journal of Therapeutics. 2009 15(5); 450 - 457

Source: Tufts CSDD analysis of 10, 038 phase I-IV protocols

Impact on Clinical Trial Performance

(All TAs, Phases II-III)

	'01 '04	'05 '08	Difference
Study volunteer screen to completion rate	52%	23%	
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. American Journal of Therapeutics. 2008 15(5); 450 - 457

Source: Tufts CSDD

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**

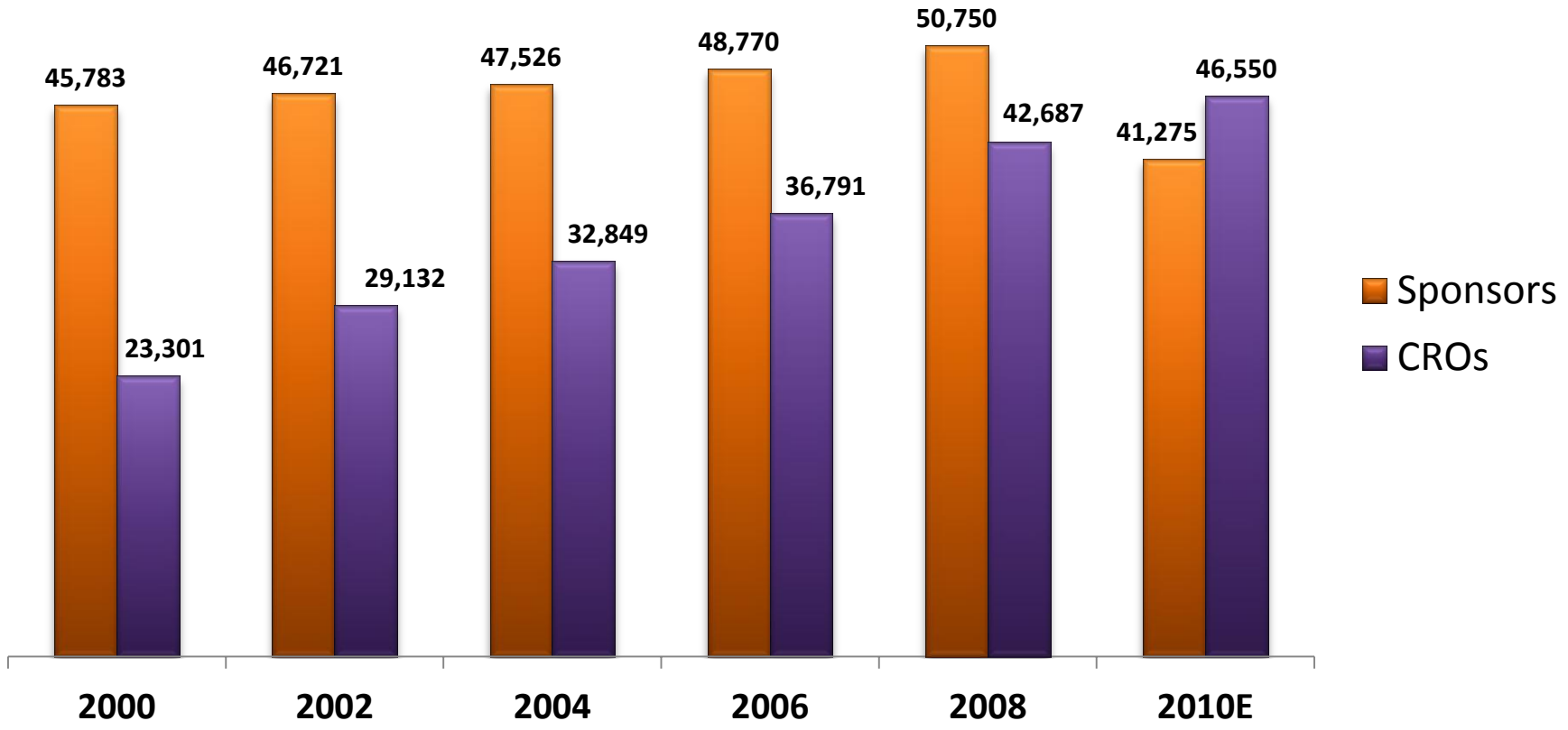
Getz et al. Measuring the Incidence, Causes and Repercussions of Protocol Amendments. Drug information Journal. 2011 45(3); 265 - 275

Source: TCSDD 2010 analysis of 3,596 amendments and 19,345 changes

Steps to Build Quality into Protocol Design

- **Identifying where and why protocol complexity is increasing -- finding opportunities to balance scientific and operating objectives**
- **Quantifying the magnitude of the problem**
  - **Detailed articulation of performance impact**
  - **Economic impact: pilot study finds that 30-40% of data collected is not relevant/never used**
- **Modifying the protocol authoring process to reduce amendments**
- **Redesigning the process to better integrate feasibility input from CROs, sites and patients**

The Integral Role of CRO Partners: Worldwide R&D Capacity



SPONSOR NET SPENDING **$3.2 BILLION** → **$11.4 BILLION**

Source: Tufts CSDD analysis of Major Pharma and CRO headcount data

Clinical Outsourcing: Becoming an Integrated Partner

Transactional Relationship	Integrated Clinical Research Alliances
Ad-Hoc	Formalized
Capacity-based	Virtual/Competency-based
Reactive, project task outsourcing	Planned, portfolio outsourcing
Shadow headcount, sponsor SOPs	Lean operation, integrated/coordinated
Mid-management governance committee	Multi-level shared governance & SOPs
Lowest-bid/Many Providers	Few Partner-Providers
High out-of-scope costs/ Fee for service	Shared operating risk/Fixed pricing

Distribution of Clinical Services Revenue by Sponsor Relationship Type

Type of Relationship	15 Largest CROs	Midsize/Niche CROs
Transactional (full, niche) services	29%	59%
Functional service provider (FSP)/Multi-FSP services	33%	19%
Integrated alliance services	39%	22%

Source: CenterWatch (N= 40 CRO companies)

Mapping CRO Usage Strategies

Functional Area	Activities/ Tasks	Proportion Keeping Inhouse	Proportion Outsourcing	Primary Relationship Models Used
Design & Planning		80%	20%	Typically Niche
Site Operations	Selection	30%	70%	Full and FSP
	Contracts & Budgets	40%	60%	Full and FSP
	Start-Up	20%	80%	Full and FSP
	Enrollment	25%	75%	Niche, Full, FSP
Data Management		25%	75%	FSP
Statistical Analysis		30%	70%	Niche, Full, FSP
Medical Writing		40%	60%	Niche, Full, FSP
Regulatory	Strategy	85%	15%	Niche
	Support	45%	55%	Niche, Full, FSP

Source: Tufts CSDD analysis of 36 major pharmaceutical and biotechnology companies

Collaborative Support Mechanisms

- Management committees at operating and senior levels
- Routine project team meetings
- Relationship management liaison role
- Regular communication
- Communication policies
  - Issue escalation & management
- Standard operating procedures and practices
- Key performance indicators
- Interim and post-project feedback

Closing Thoughts

- **Not only tailoring protocol design to mitigate clinical trial process risk; but also about applying QRM and QbD principles into protocol design process itself**
    - **Role for greater agency input and standards**
- **Parties on the front line and with rich, multi-sponsor breadth of experience (CROs and investigative site personnel) need a seat at the table**

Q&A and THANK YOU!

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